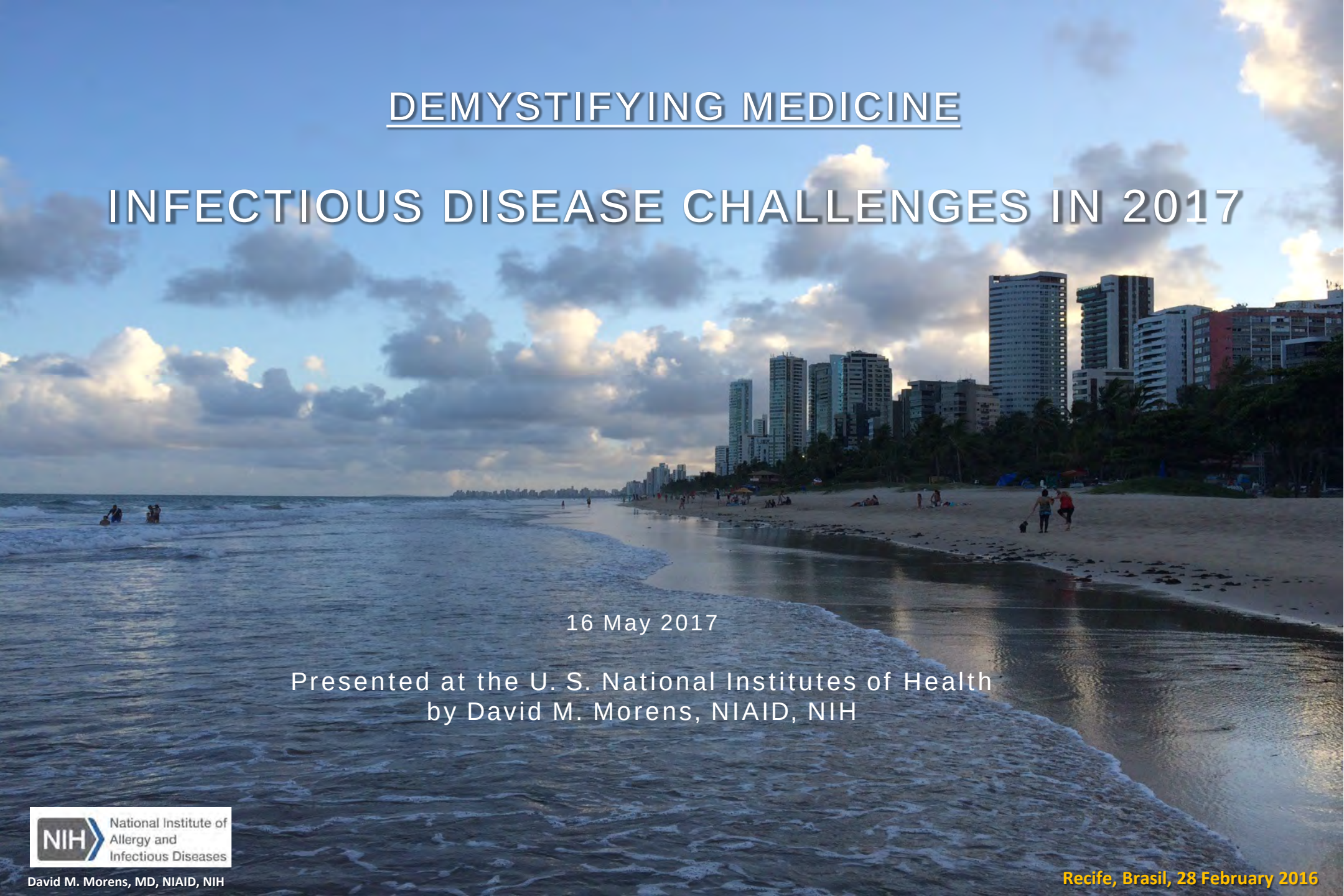


# DEMYSTIFYING MEDICINE

# INFECTIOUS DISEASE CHALLENGES IN 2017

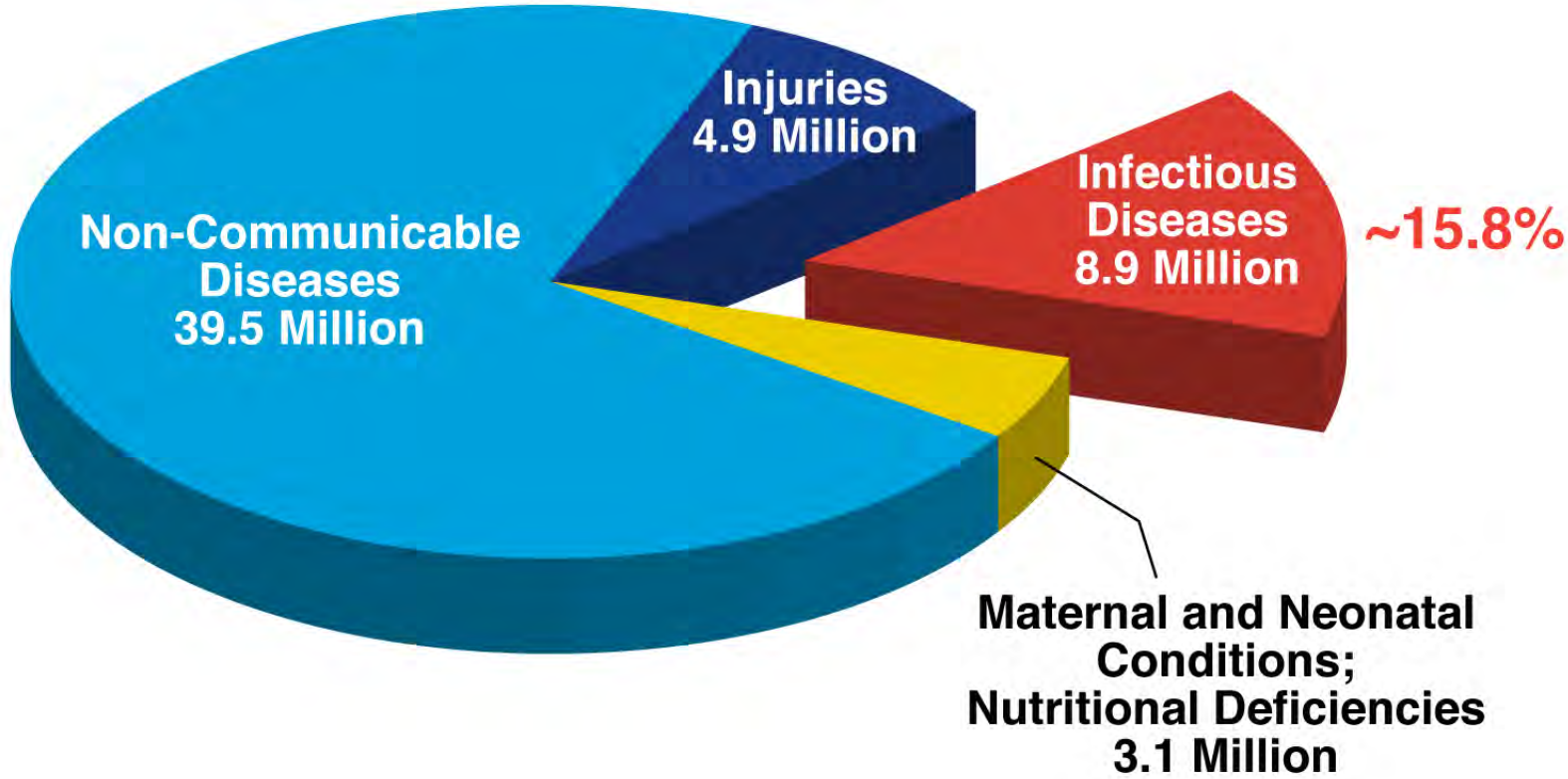
16 May 2017

Presented at the U. S. National Institutes of Health
by David M. Morens, NIAID, NIH

National Institute of Allergy and Infectious Diseases
David M. Morens, MD, NIAID, NIH

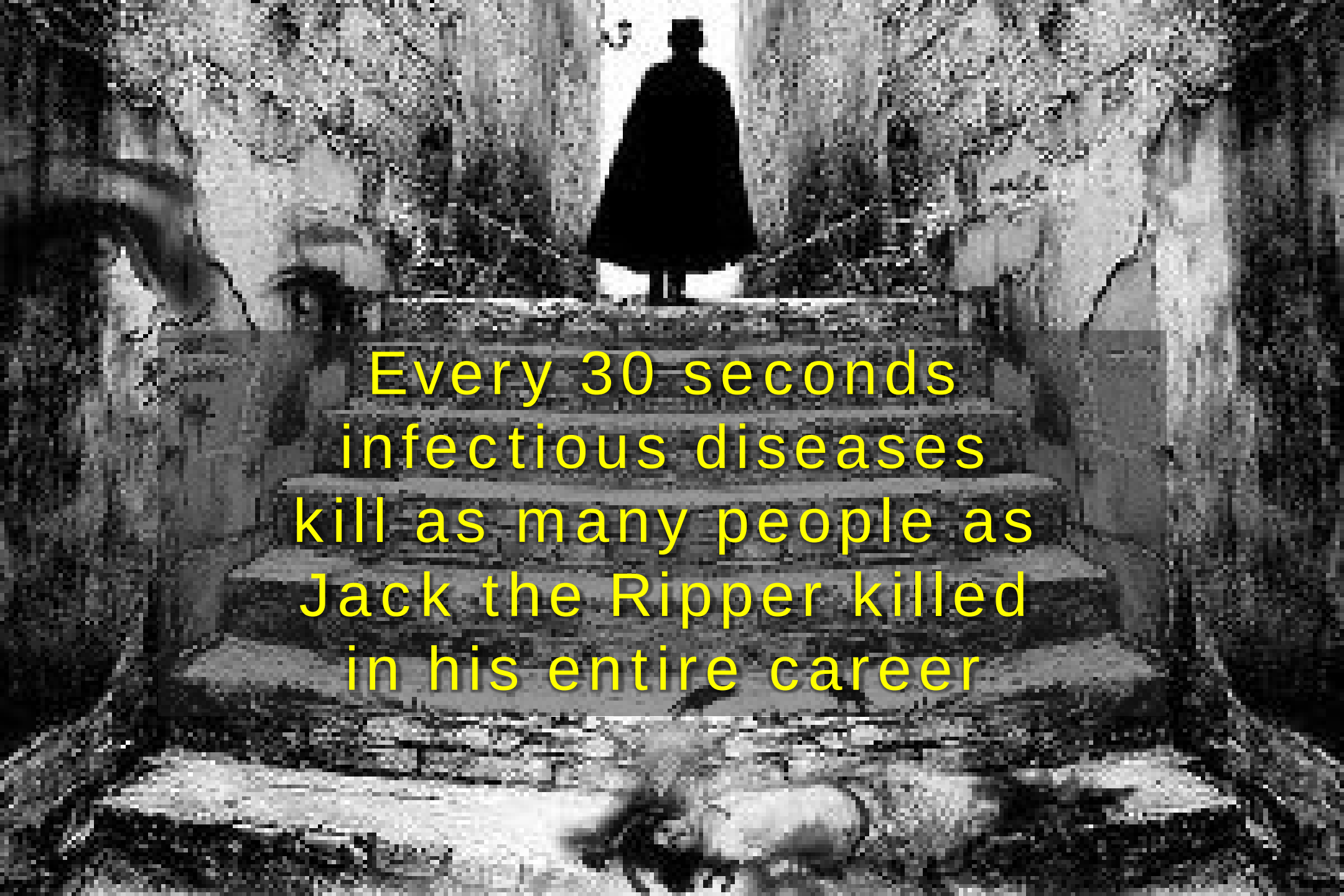
Recife, Brasil, 28 February 2016

# Infectious Diseases Caused ~16% of All Deaths Worldwide in 2015




**Estimated Total Deaths (2015): 56.4 Million**

Source: WHO, 2017.


Every 30 seconds
infectious diseases
kill as many people as
Jack the Ripper killed
in his entire career

# Global Health and Infectious Diseases

- Established Infectious Diseases
- Newly Emerging Diseases
- Re-Emerging Diseases

# Examples of Established Infectious Diseases of Global Health Importance

| | Estimated Deaths, 2015 |
|---|---|
| Lower Respiratory Infections | 3.2 M |
| Tuberculosis | 1.4 M |
| Diarrheal Diseases | 1.4 M |
| Hepatitis B & C | 1.3 M |
| HIV/AIDS | 1.1 M |
| Malaria | 429,000 |
| Meningitis | 315,000 |

Source: WHO, 2017.

# The Global Burden of Malaria, 2015

- 429,000 malaria deaths, 92% in Africa
- 212 million new malaria cases
- Ongoing transmission in 91 countries/areas

- Every two minutes a child <5 years dies from malaria

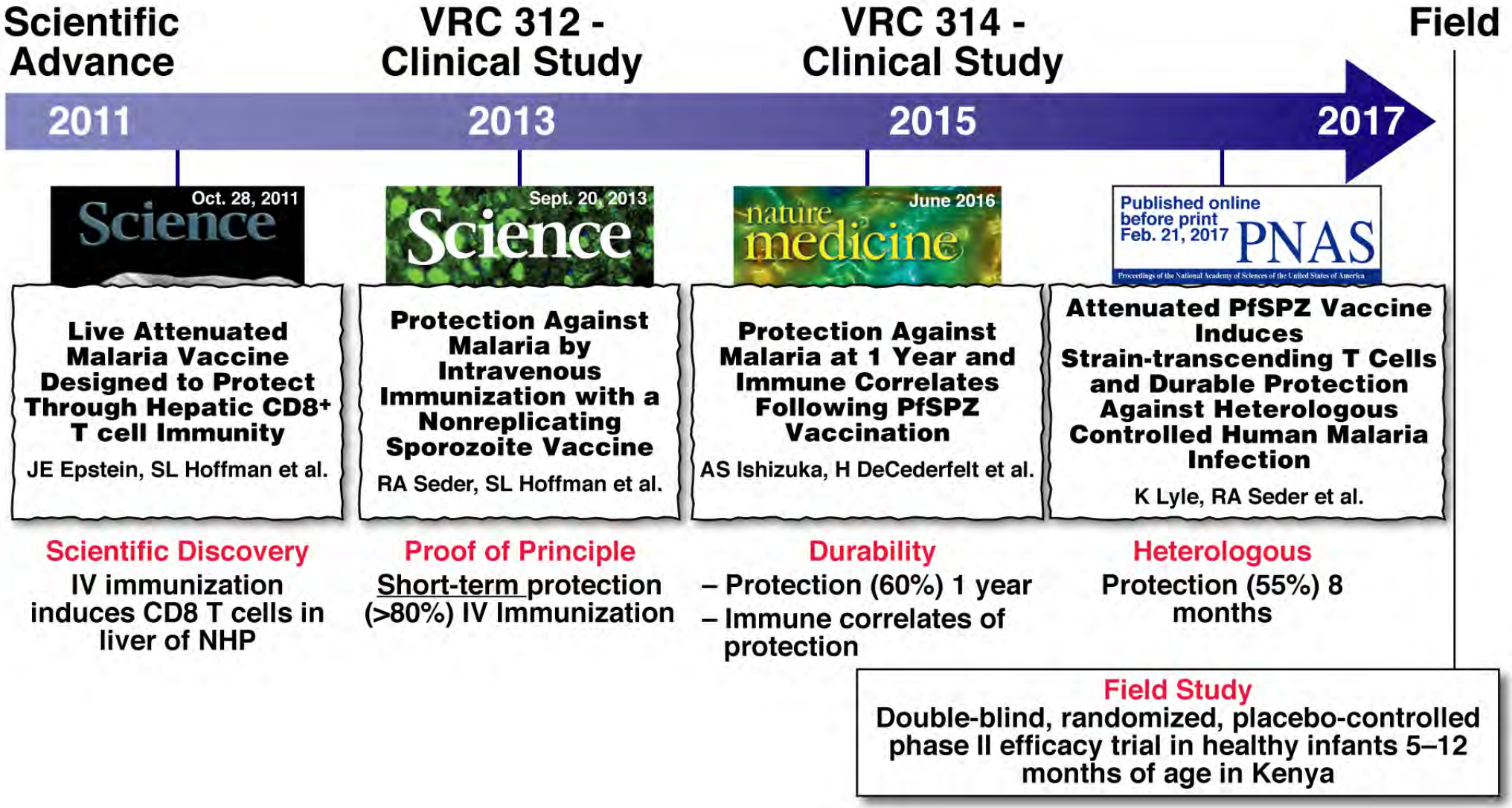
Source: WHO, World Malaria Report 2016

# Progress in Fighting Malaria, 2000-2015

- Scale-up of key interventions
  - Insecticide-treated mosquito nets
  - Indoor residual spraying
  - Rapid diagnostic testing
  - Artemisinin-based combination therapy (ACT)
  - Intermittent preventive treatment in pregnancy
- 41% decline in incidence rate
- 60% decline in malaria deaths
- 6.8 million lives saved
- 17 countries eliminated malaria

Source: WHO

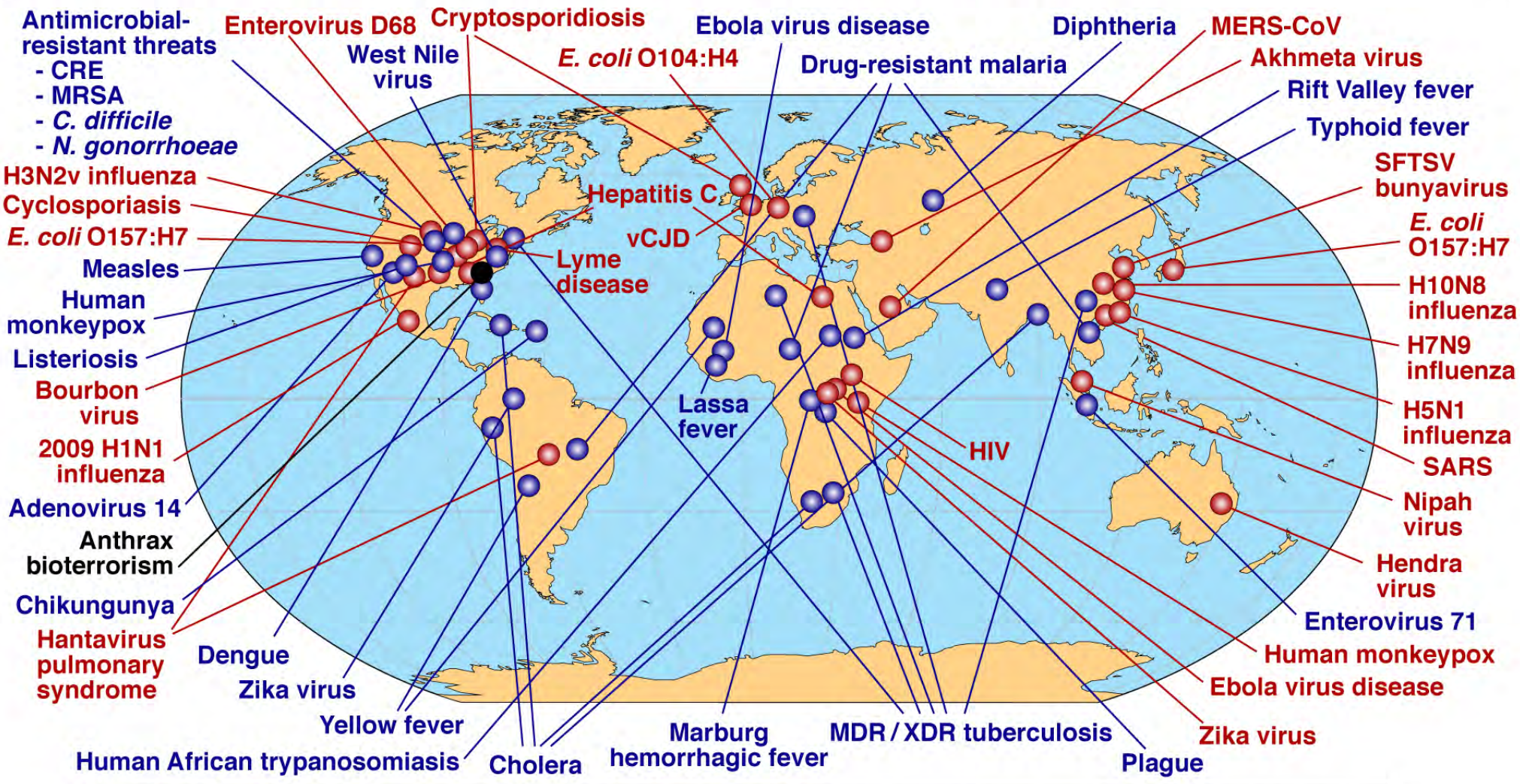
# Scientific / Clinical Development of PfSPZ Vaccine



# Global Health and Infectious Diseases

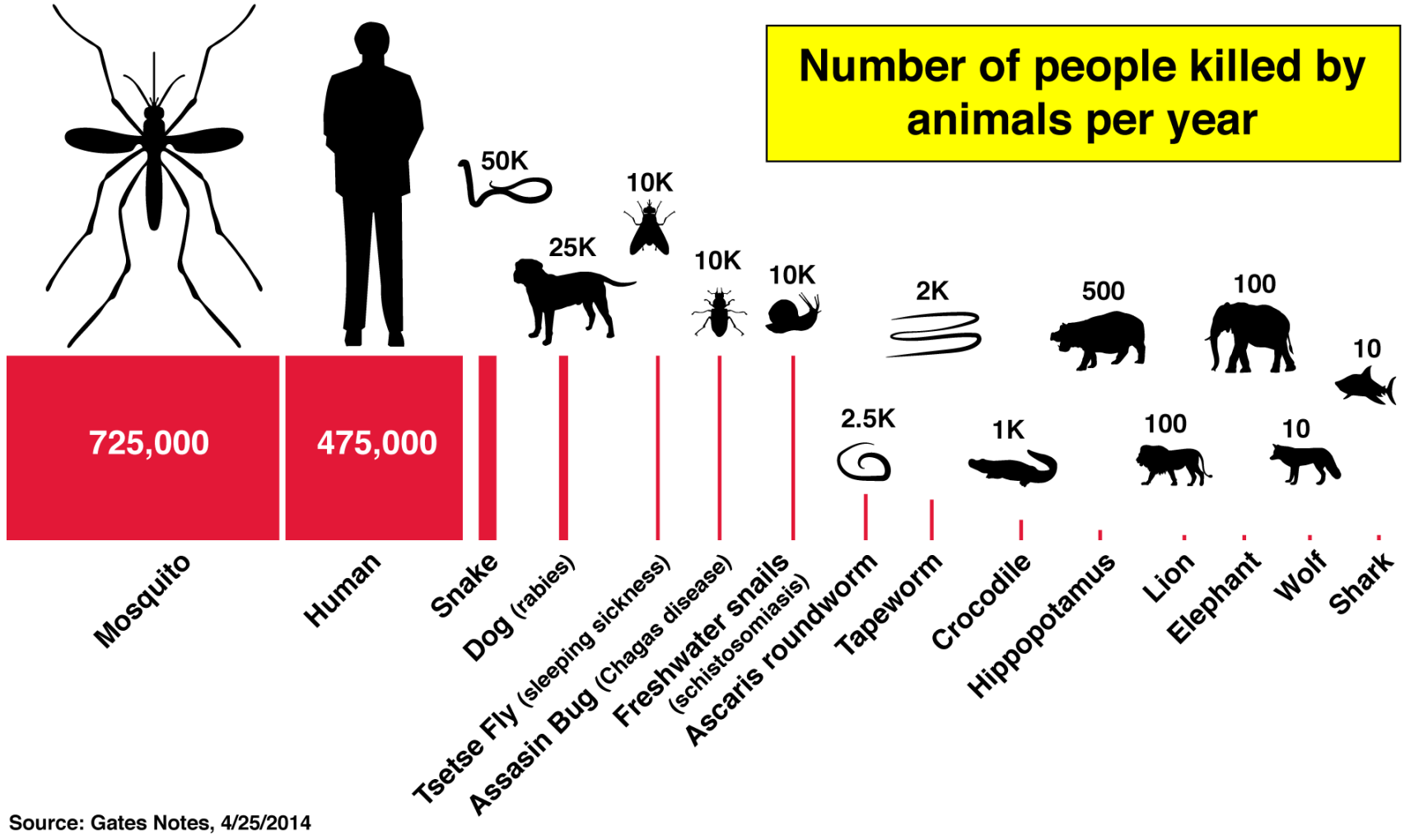
- Established Infectious Diseases
- Newly Emerging Diseases
- Re-Emerging Diseases

# Global Examples of Emerging and Re-Emerging Infectious Diseases




December 2015

# World's Deadliest Animals




Source: Gates Notes, 4/25/2014

# DETERMINANTS OF DISEASE EMERGENCE

1 – Microbial adaptation & change

2 – Human susceptibility to infection

3 – Climate and weather

4 – Changing ecosystems

5 – Human demographics/behavior

6 – Economic development/land use

7 – International trade/commerce

8 – Technology and industry

9 – Breakdown of PH measures

10 – Poverty and social inequality

11 – War and famine

12 – Lack of political will

13 – Intent to harm

Morens, et al. *Lancet Infect Dis* 2008;8:710-719

# Recently Emerging Human Arboviral Diseases in the Americas

| | |
|---|---|
| Dengue | 1990s |
| West Nile | 1999 |
| Chikungunya | 2013 |
| Zika | 2015 |
| Yellow Fever | 2016 |

Others: Bourbon, Cache Valley, Heartland, Itaqui, Mayaro, Oropouche, Powassan

Source: PF Vasconcelos & CH Calisher, *Vector Borne Zoonotic Dis* 16:295, 2016.

JOURNAL OF MEDICAL ENTOMOLOGY

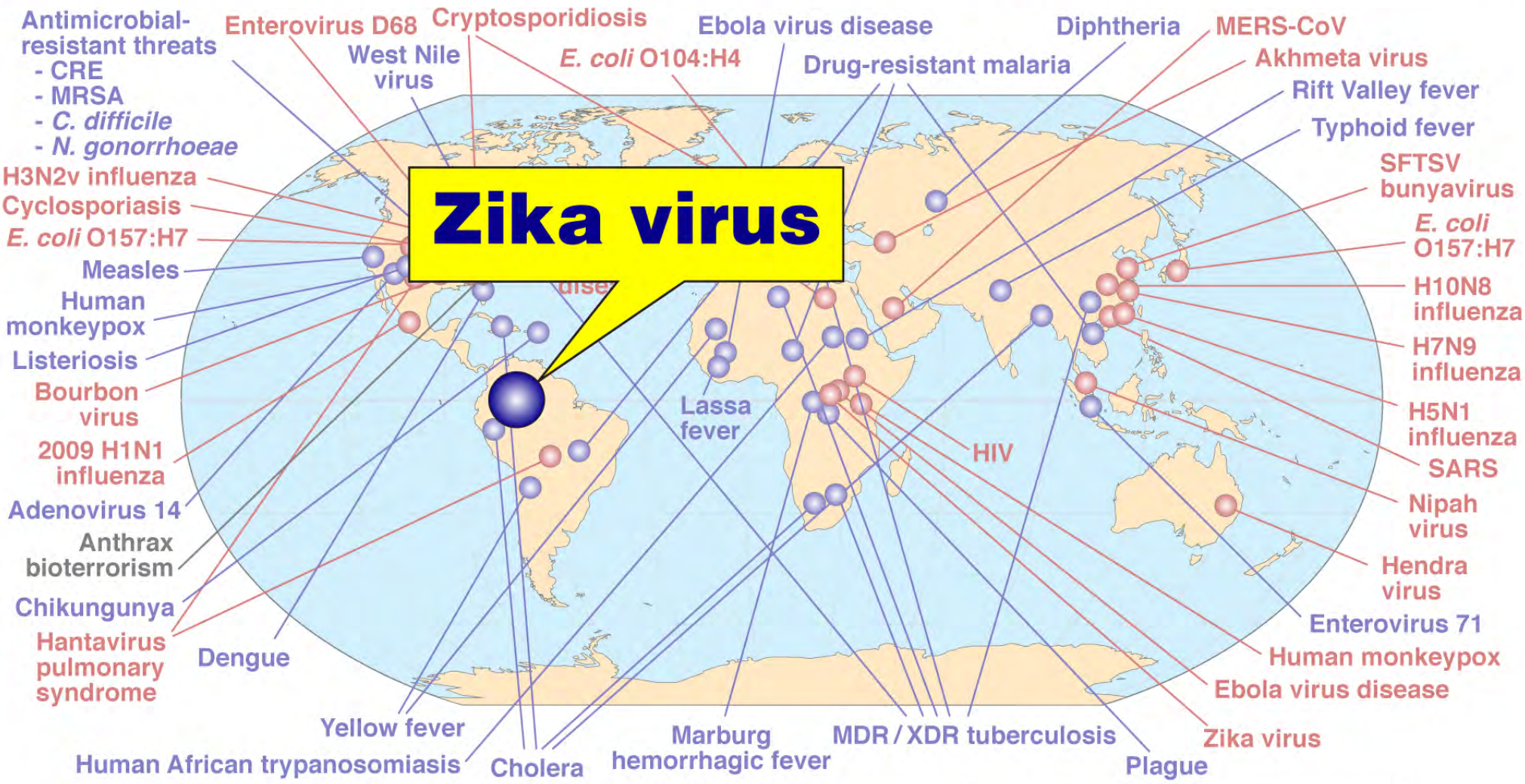
Published online March 2, 2017

# Emergent and Reemergent Arboviruses in South America and the Caribbean: Why So Many and Why Now?

CB Marcondes et al.

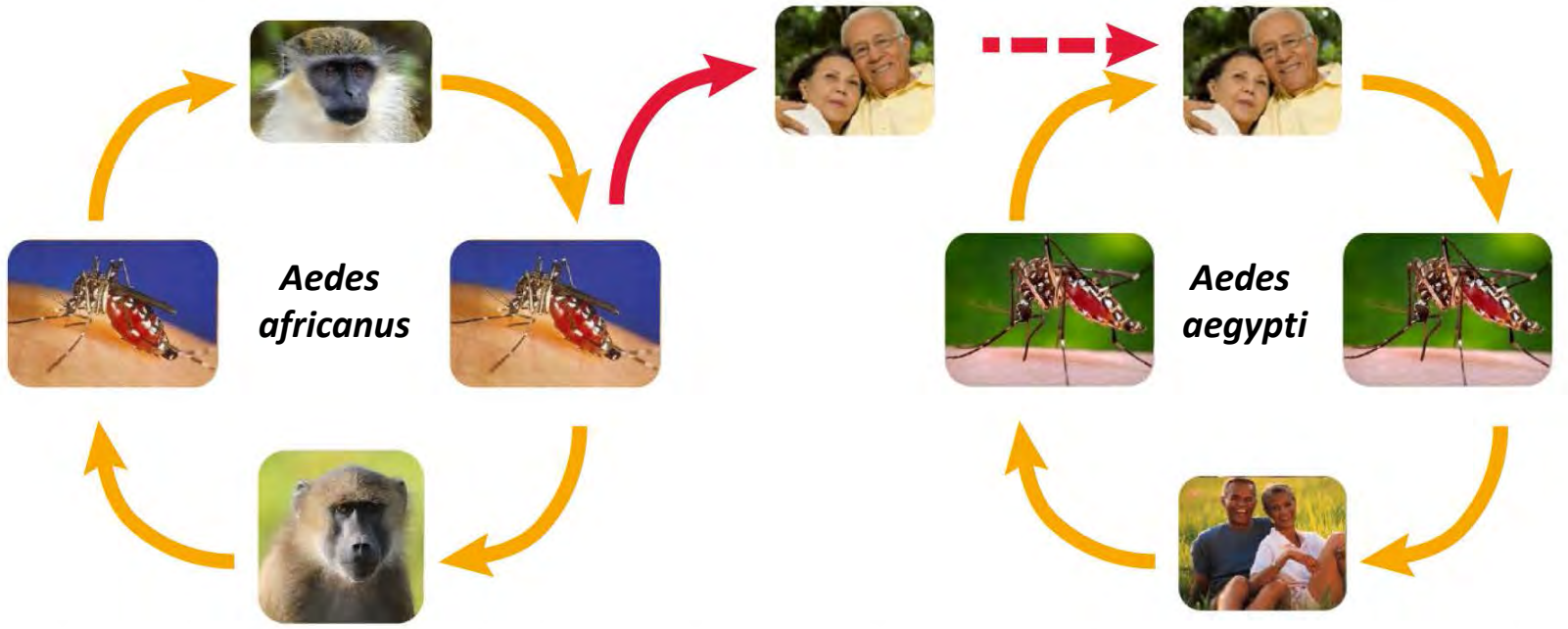
- Availability of vectors and hosts (e.g. >860 mosquito species in S. America)
- Changing climate and vegetation
- Increased international travel and commerce
- Urbanization

# Global Examples of Emerging and Re-Emerging Infectious Diseases




December 2015

# Zika Virus Transmission Cycles



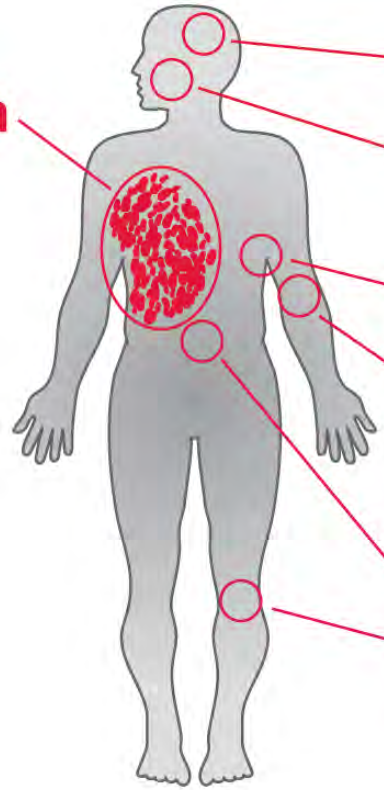

Source: CDC

# Symptoms of Zika Virus Infection

- 4 in 5 individuals *asymptomatic*

**Incubation**
**3-12 days**

**Mild symptoms**
**2-7 days**



Rash

Headache/Malaise

Non-purulent conjunctivitis/
Conjunctival hyperemia

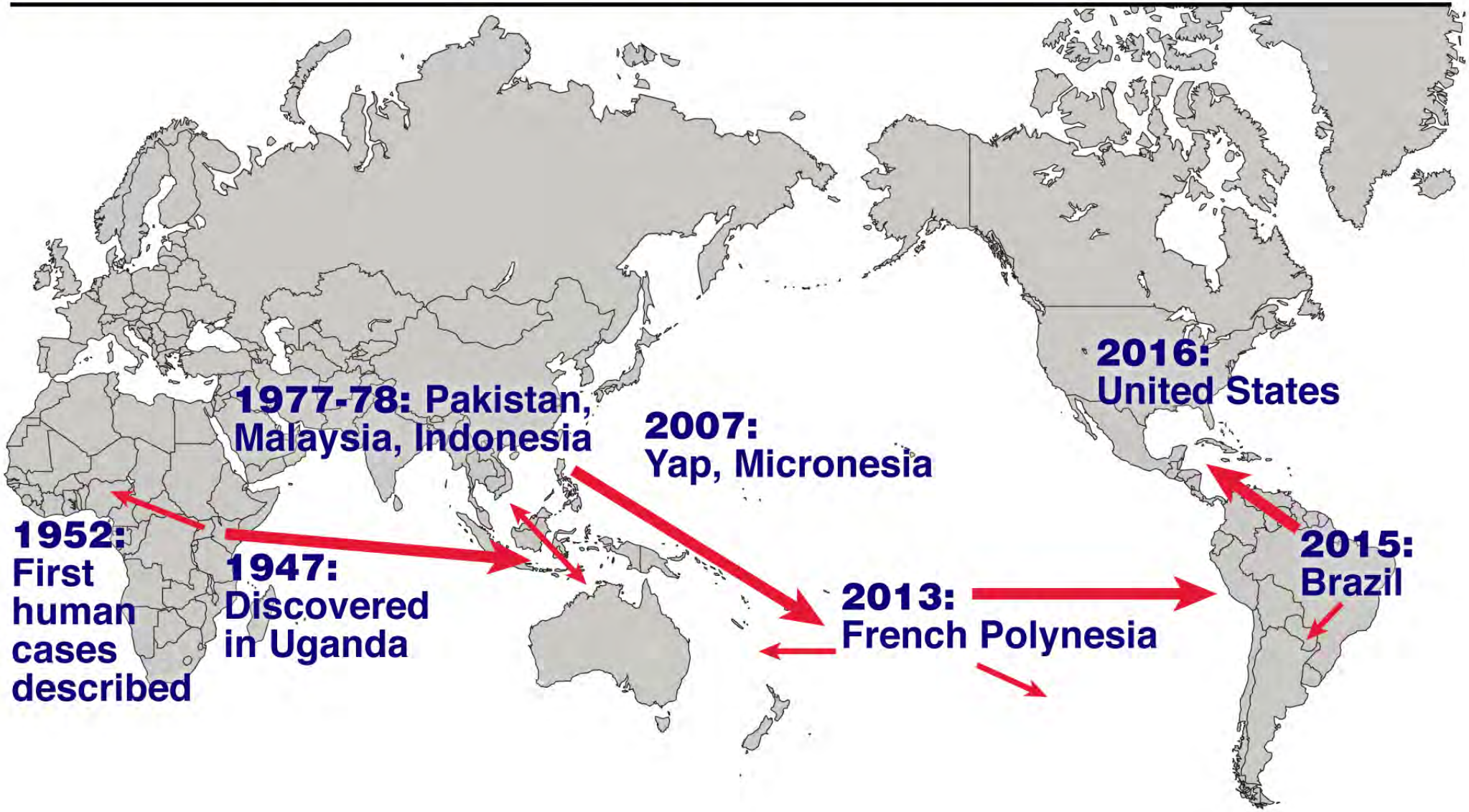
Elevated body temperature
(Above 99°F)

Arthralgia/Myalgia

Peripheral edema/gastrointestinal
disturbance have also been observed

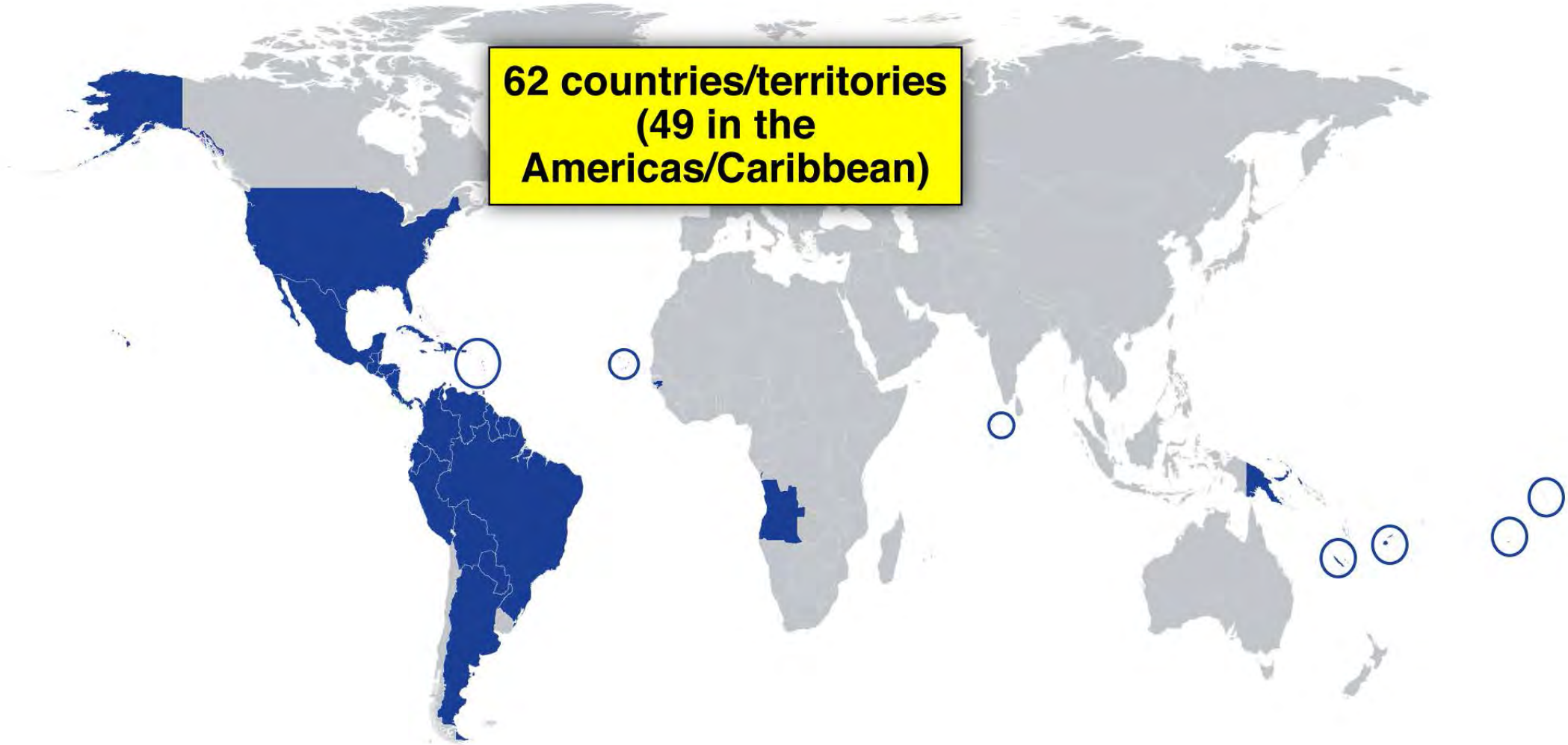
Source: BMJ.com, 2/2016

# Zika Virus Spread, 1947-2017



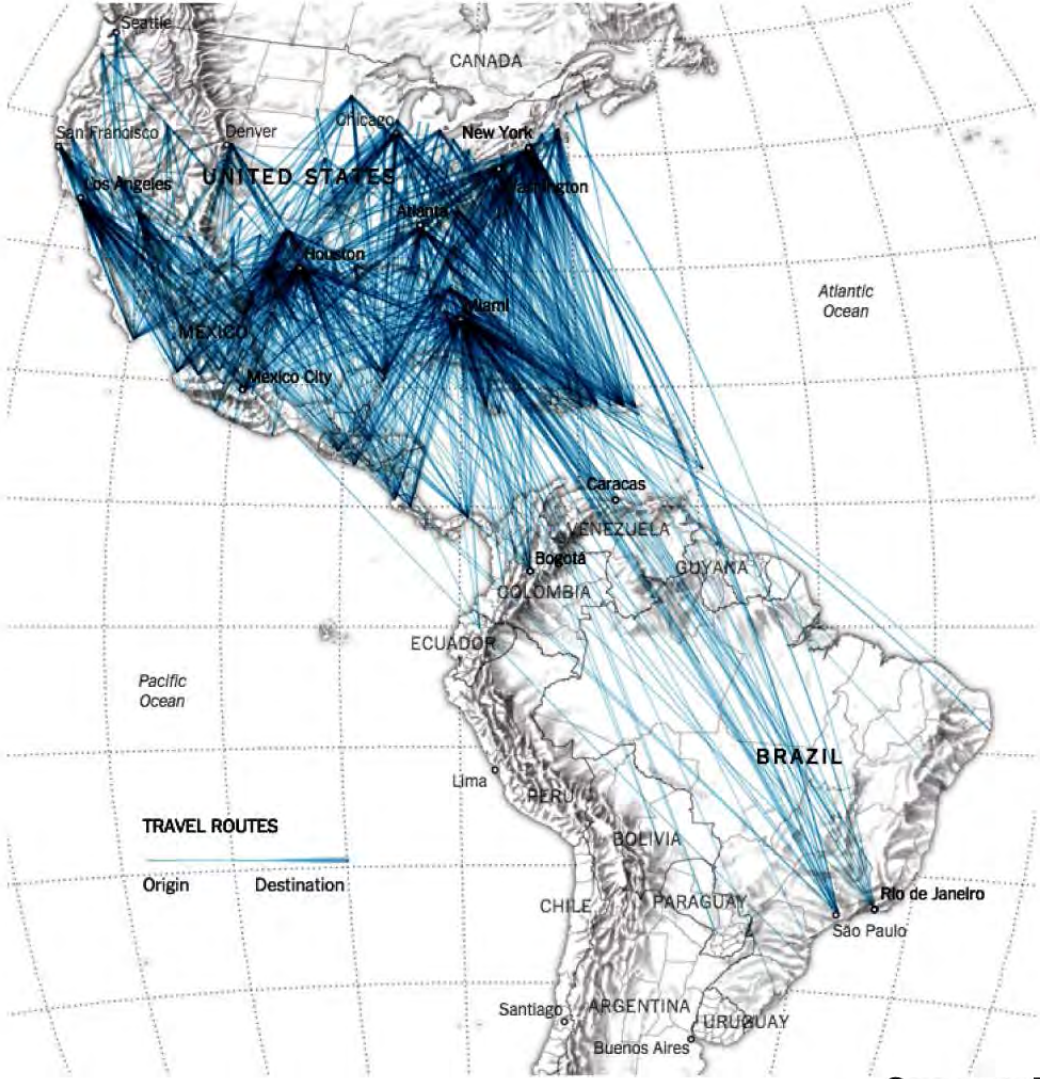

Source: Lancaster University

# Countries and Territories with Recent Local Zika Virus Transmission - May 2017




Source: CDC

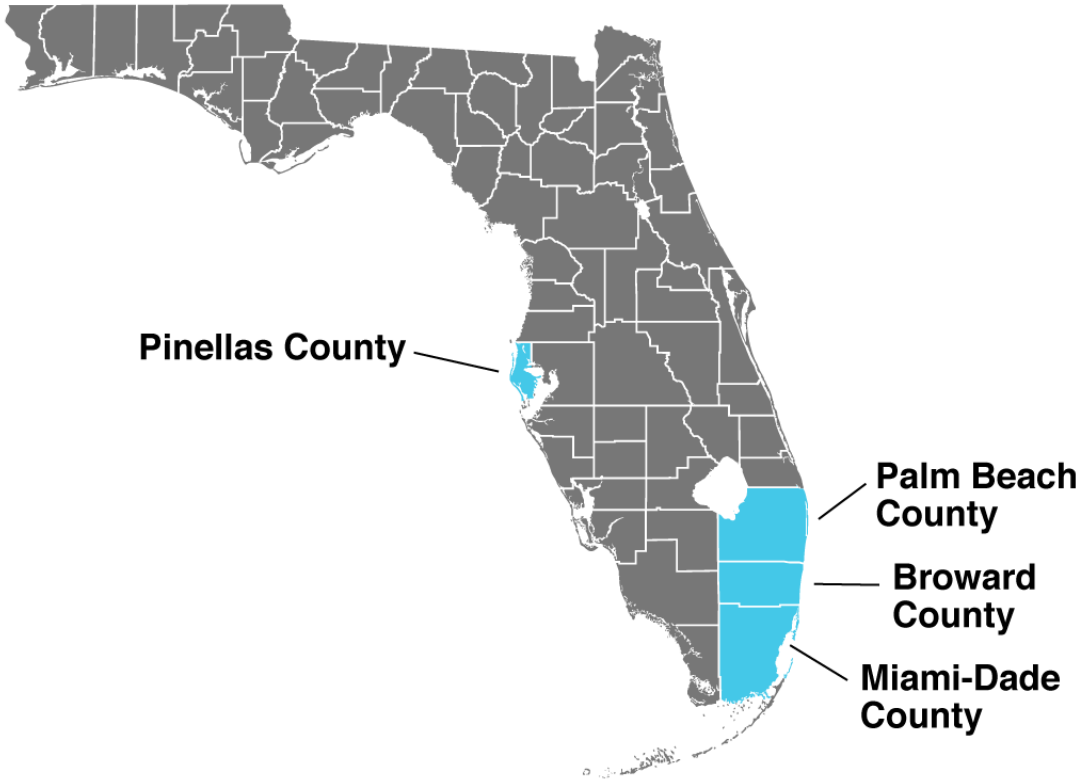
# Potential for Imported Cases of Zika in the United States



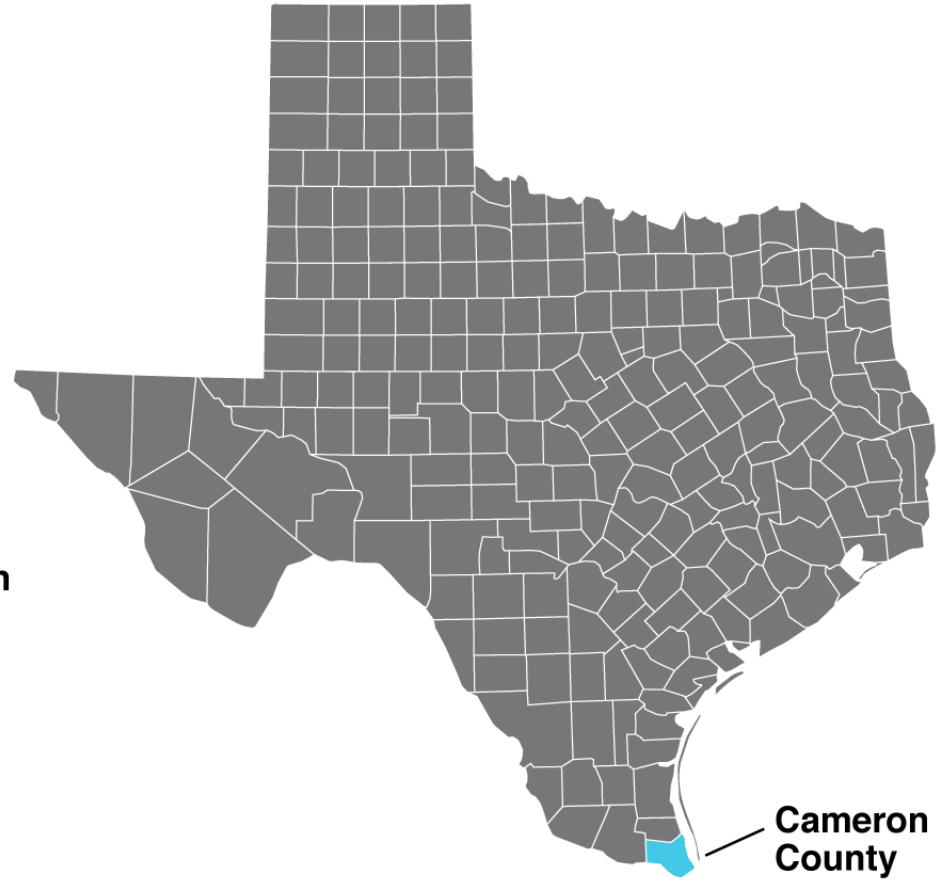

- **~216 million passenger journeys to U.S. annually from areas with local Zika virus transmission**
  - **– 34 M by air**
  - **– 173 M by land**
  - **– 9 M by sea**

**Sources: B Nelson et al. *PLoS Currents Outbreaks*, 5/31/2016; NY Times.**

# Locally Acquired Mosquito-Borne Zika Infections in Florida and Texas, 2016-2017




**N=218**




**N=6**

Source: CDC, data as of May 3, 2017

# Reported Cases of Zika Virus Disease in the United States, 2015–2017

- **U.S. States / District of Columbia**

  **– 5,273 cases**

  - 5,001 travel-associated
  - 224 locally acquired mosquito-borne
  - 46 sexually transmitted, 29 congenital
  - 1 laboratory-acquired, 1 unknown

- **U.S. Territories**

  **– 36,581 cases**

  - 36,438 locally acquired
  - 143 travel-associated

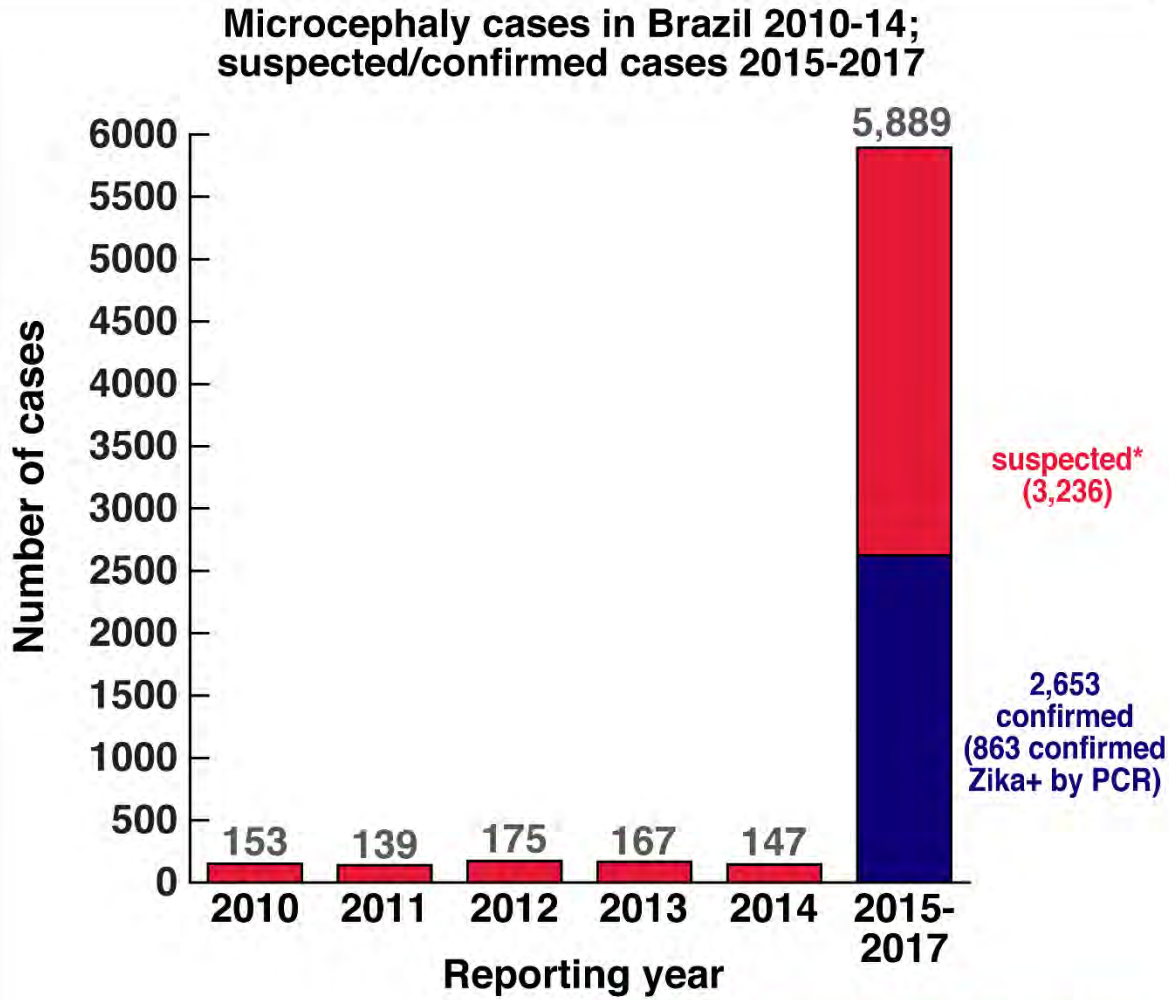
Source: CDC, data as of May 10, 2017

# Marked Increase in Microcephaly Cases in Brazil

Associated Press

November 30, 2015

## Brazil Links Mosquito-Borne Zika Virus to Microcephaly Birth Defect




Source: Brazilian MOH; data as of April 26, 2017

Published online
November 03, 2016

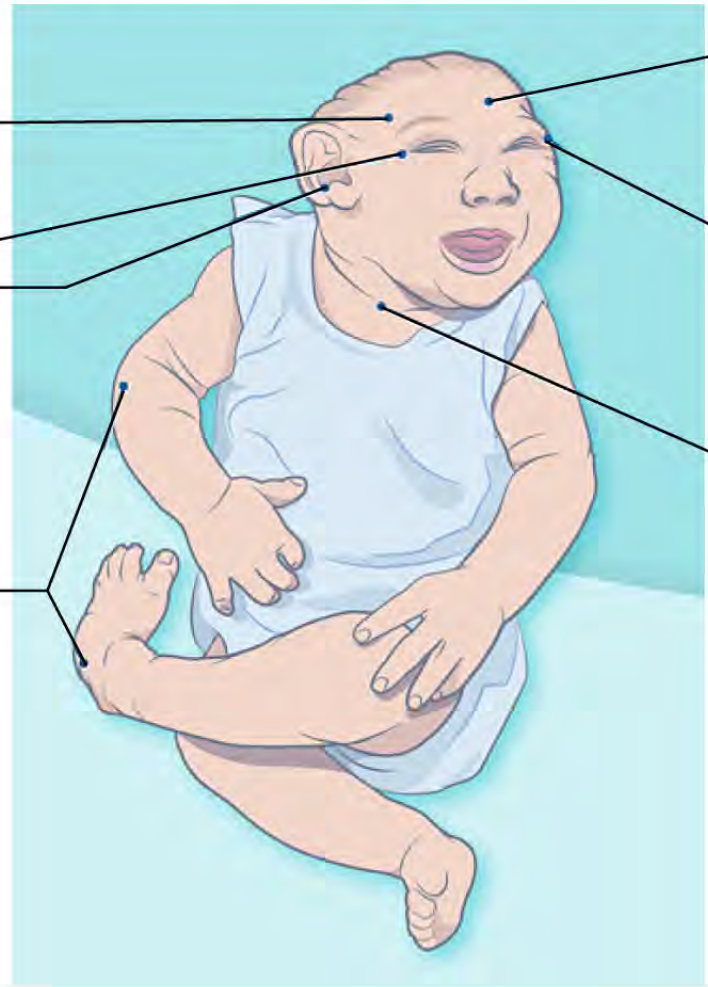
JAMA Pediatrics

# Characterizing the Pattern of Anomalies in Congenital Zika Syndrome for Pediatric Clinicians

CA Moore, SA Rasmussen et al.

***"Congenital Zika syndrome** is a recognizable pattern of structural anomalies and functional disabilities secondary to central and, perhaps, peripheral nervous system damage."*

# Congenital Zika Syndrome is a Pattern of Birth Defects in Babies Infected with Zika During Pregnancy




Source: CDC

# Zika-Affected Pregnancies and Outcomes in the United States, 2015-2017

- **U.S. States / District of Columbia**
  - **– 1,793 pregnancies**
    - 1,409 completed pregnancies with or without birth defects
    - 58 liveborn infants with birth defects
    - 8 pregnancy losses with birth defects
- **U.S. Territories**
  - **– 3,700 pregnancies***

*CDC is not reporting numbers for adverse pregnancy outcomes in the territories at this time

Source: CDC, data as of April 25, 2017

# Reported Complications of Zika Virus Disease in Adults

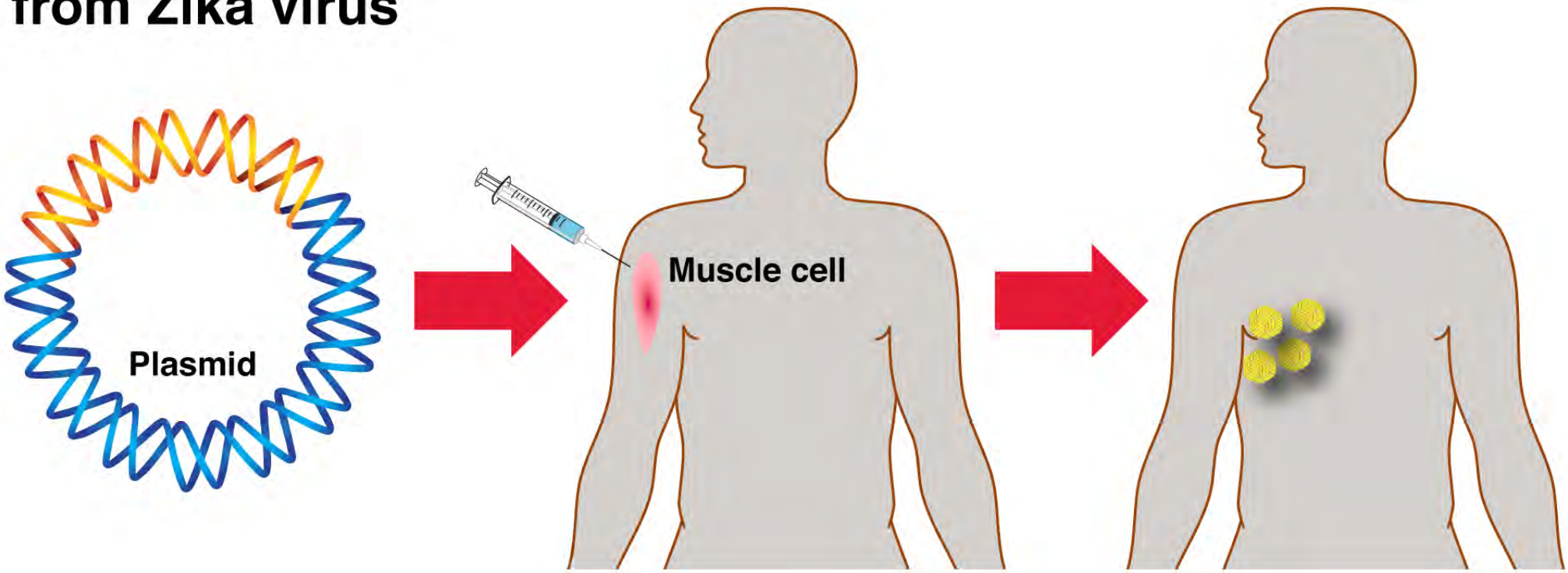
- Guillain-Barré syndrome
- Myelitis
- Meningoencephalitis/encephalomyelitis
- Uveitis
- Hearing impairment
- Thrombocytopenia
- Heart disease

# DNA Vaccine Approach

Gene encoding surface protein from Zika virus

Inject DNA containing Zika gene

Body's cells produce virus-like particles, the basis of the vaccine



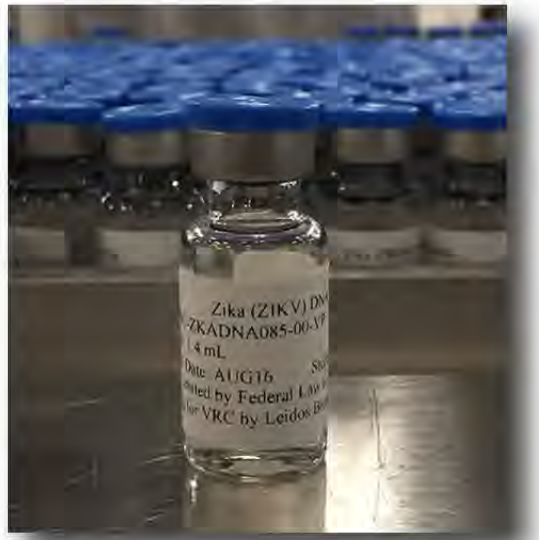
National Institutes of Health
*Turning Discovery Into Health*

**FOR IMMEDIATE RELEASE**
**Friday, March 31, 2017**

**News Release**

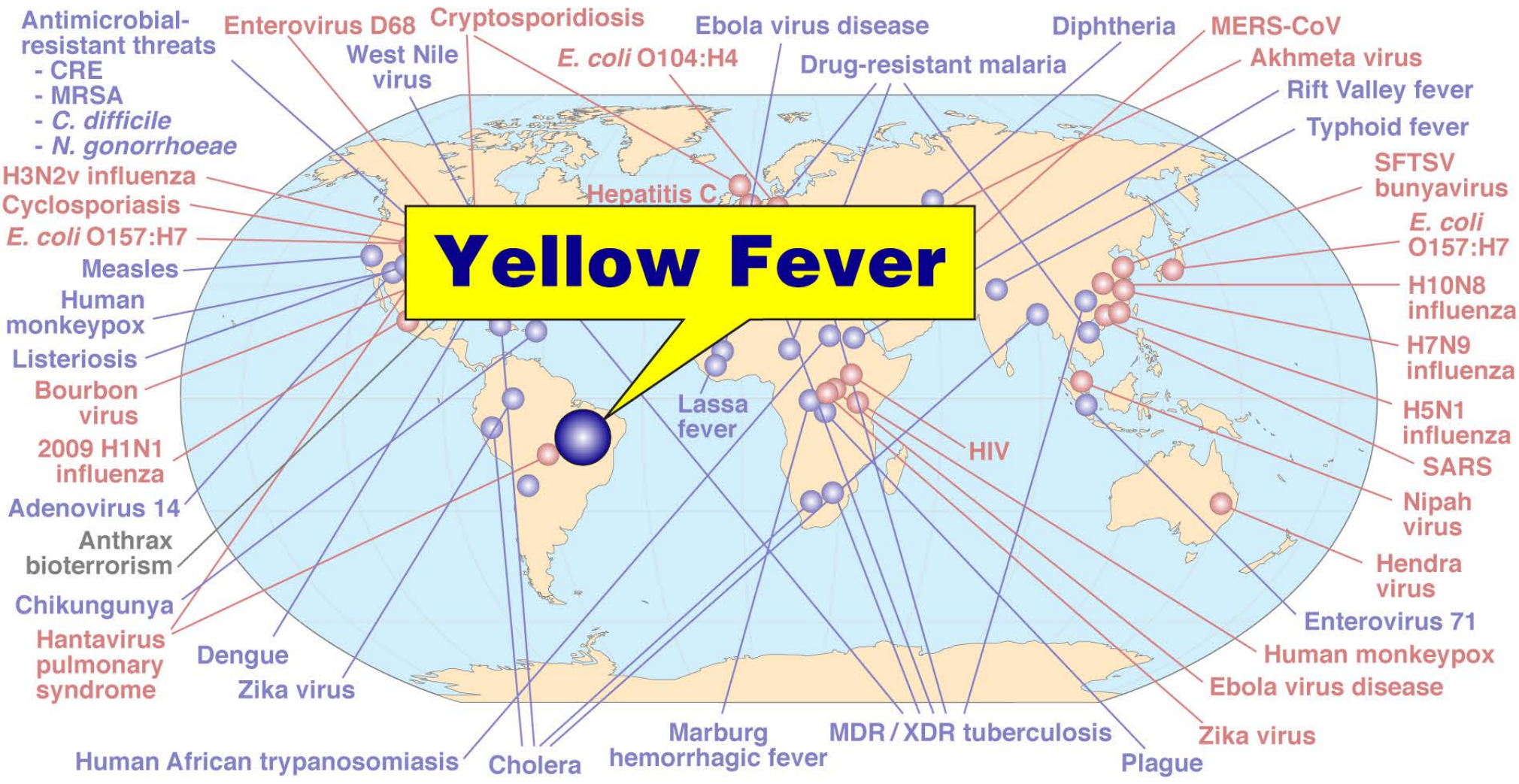
# Phase 2 Zika Vaccine Trial Begins in U.S. and Central and South America

## *Study Will Evaluate NIH's Experimental DNA Vaccine*




- **Enrollment target: at least 2,490 individuals in the continental United States, Puerto Rico, Brazil, Peru, Costa Rica, Panama and Mexico**

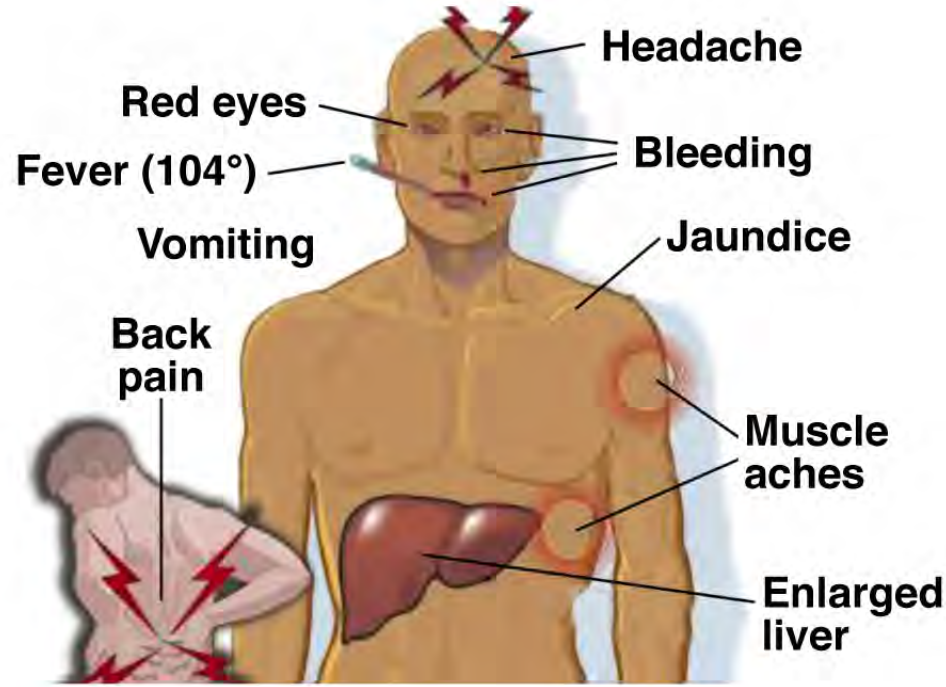
# Global Examples of Emerging and Re-Emerging Infectious Diseases



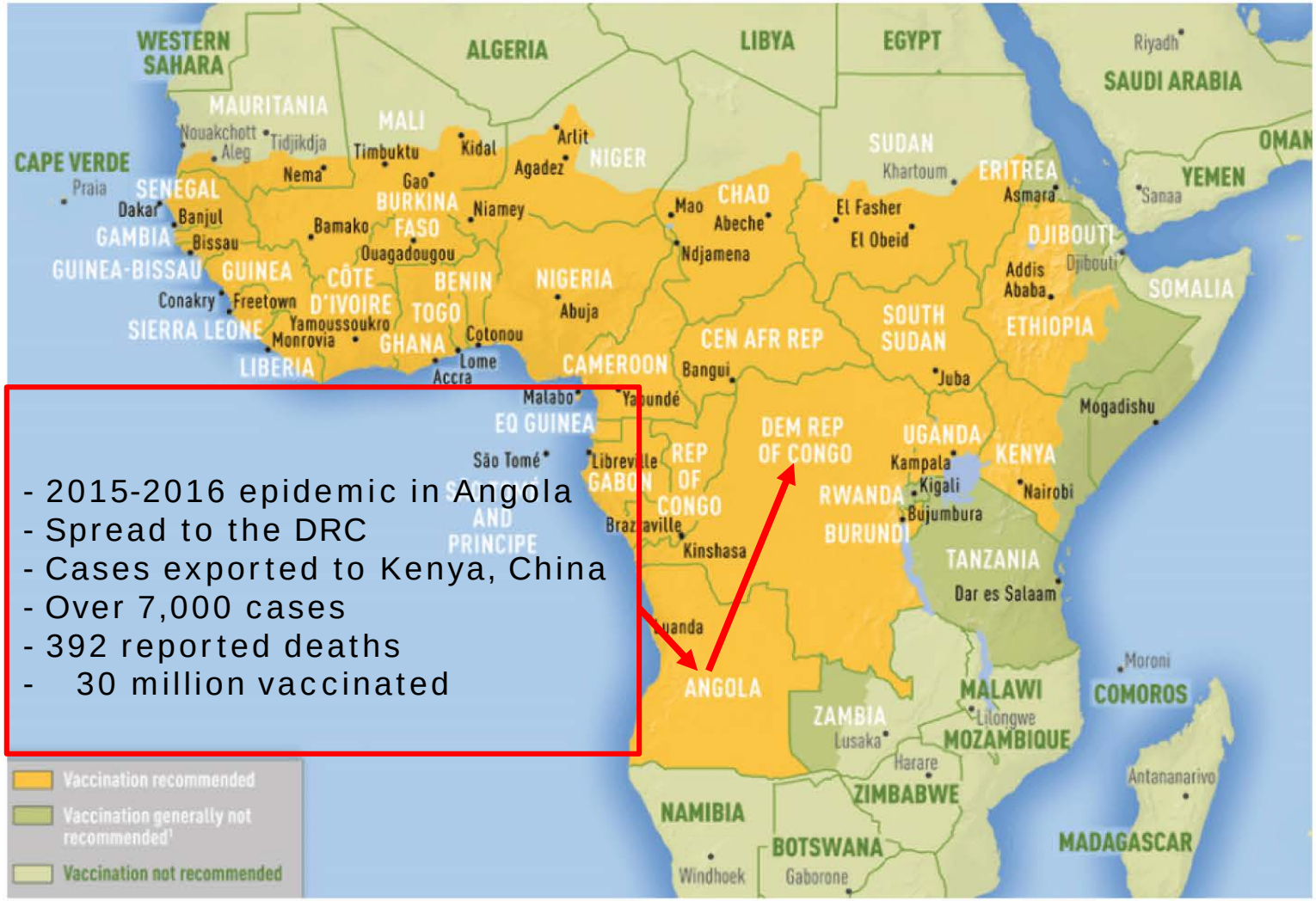

December 2016

# Clinical Manifestations of Yellow Fever (The original hemorrhagic fever)

- Incubation period: 3-6 days
- Three clinical stages:
  - Period of infection
  - Period of remission
  - Period of intoxication
    - 20-60% mortality rate

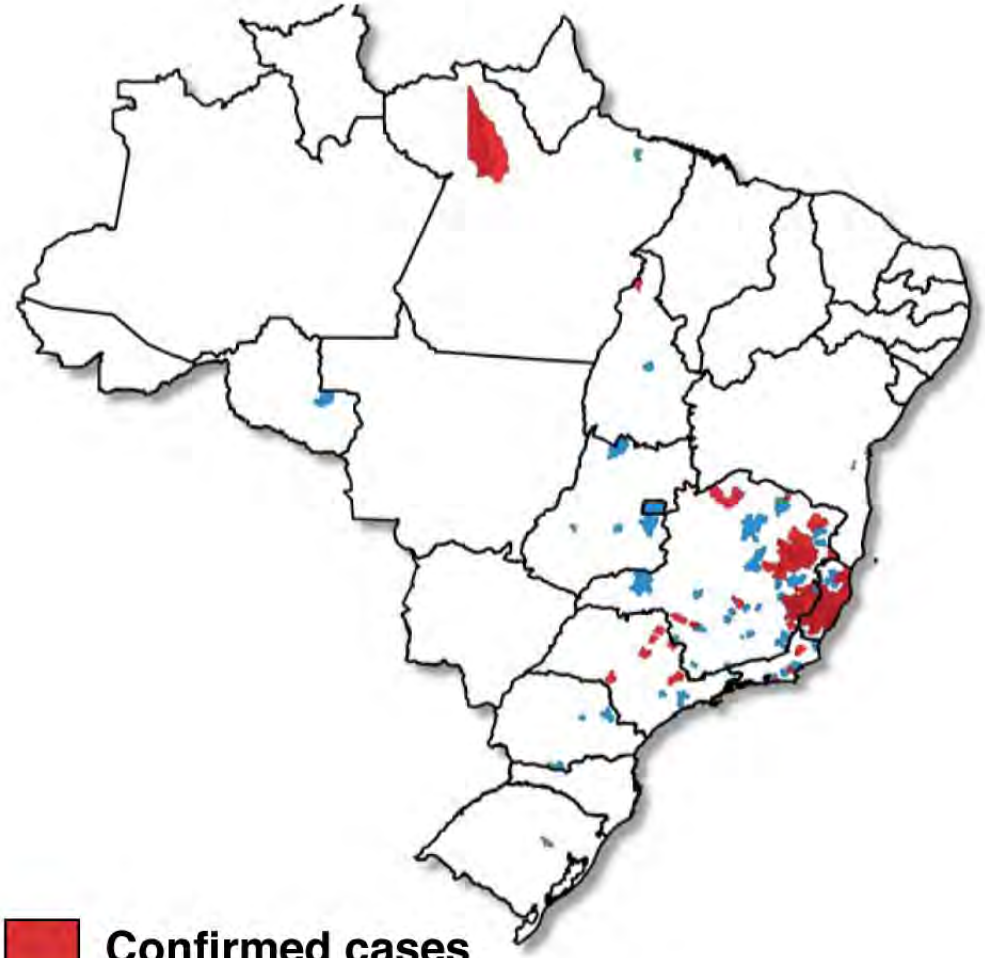


# Areas at Risk for Yellow Fever Transmission: Africa




Source: CDC 2016

# Yellow Fever in Brazil, December 2016 to May 11, 2017



Confirmed cases

Cases under investigation

- 756 confirmed cases, 622 under investigation
- 259 confirmed deaths, 47 under investigation
- Case-fatality rate for confirmed cases: 34%

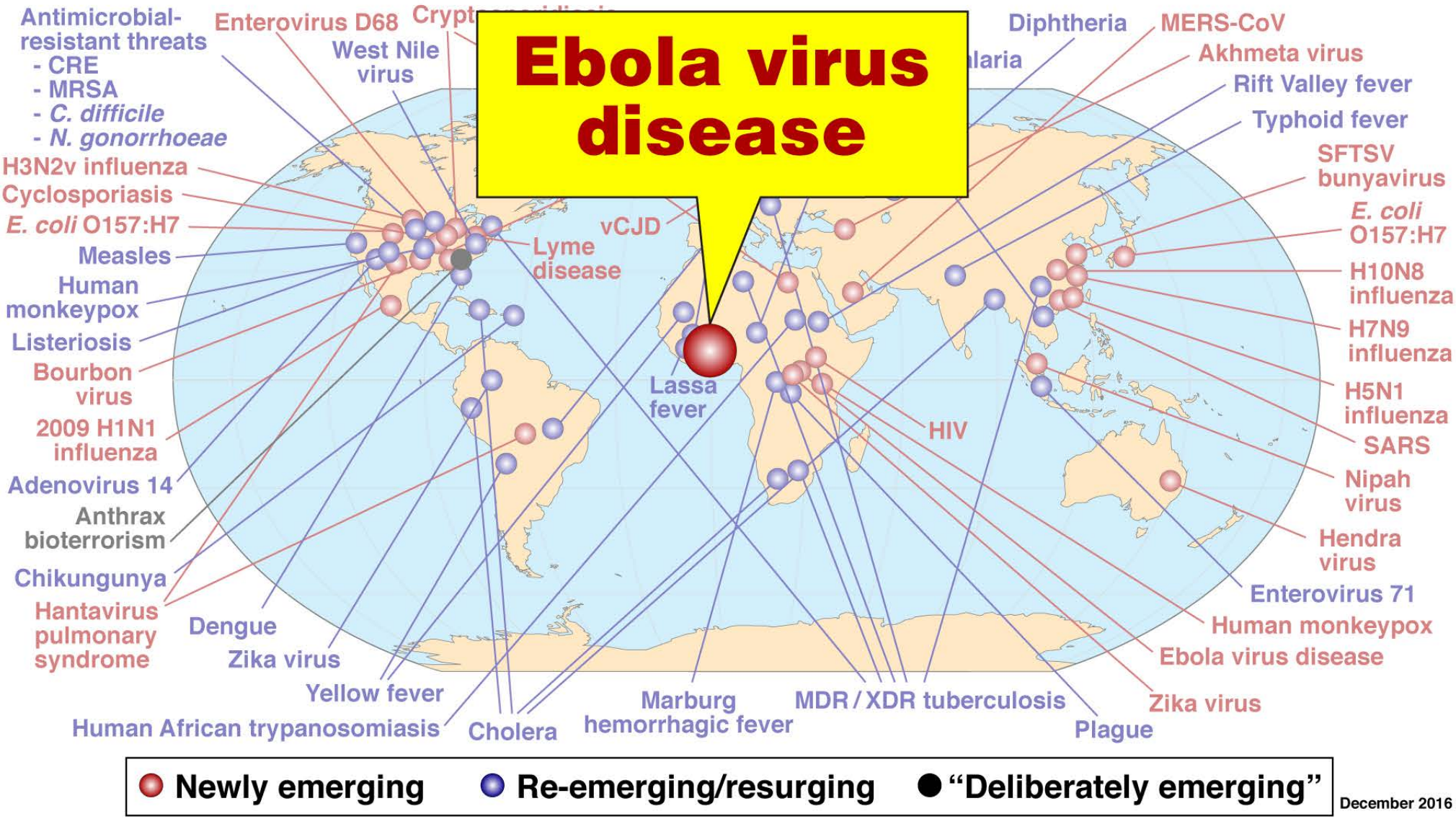
Source: Brazil MOH

# Yellow Fever Outbreak Control: Vaccination

- **Current vaccine supply:**
  - Six worldwide manufacturers
  - Worldwide stockpile of six million doses*
  - One manufacturer in the United States
- **Improving vaccine supply in an outbreak setting:**
  - Increase manufacturing capacity
  - Increase number of stockpiled doses
  - Fractional dosing
  - New vaccines

*30 million doses were used in the Angola/DRC epidemic

# Global Examples of Emerging and Re-Emerging Infectious Diseases




December 2016

# Reported Ebola Virus Disease Cases in Guinea, Liberia, and Sierra Leone, 2014-2016

**Guinea**
3,814 cases / 2,544 deaths

**Sierra Leone**
14,124 cases / 3,956 deaths

**Liberia**
10,678 cases / 4,810 deaths

**Total*:**
**28,616 cases**
**11,310 deaths**

**40% mortality**

*Confirmed, probable and suspected cases

Source: WHO, 12/2016

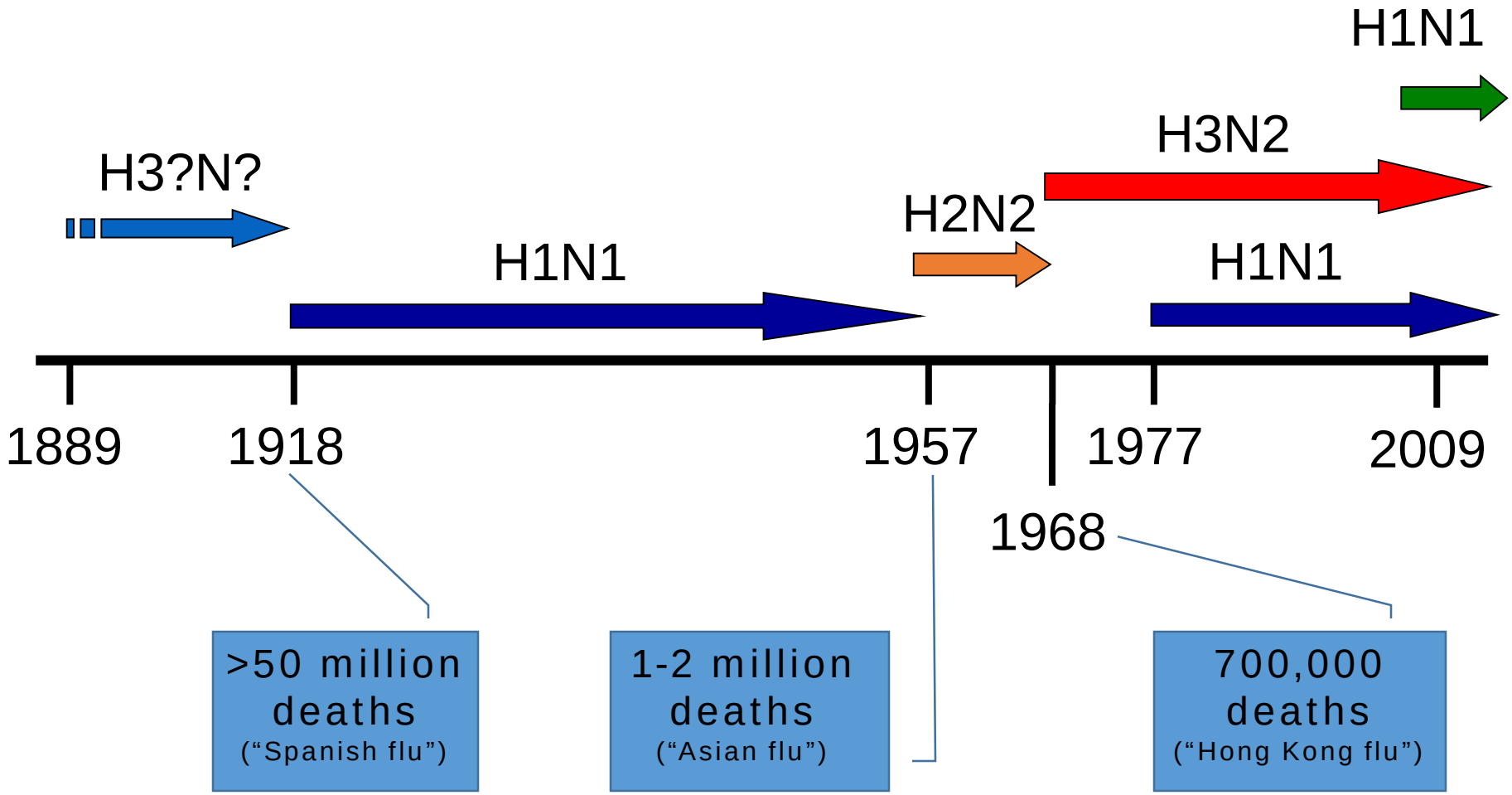
# PREVAIL Ebola Research

- **PREVAIL (Partnership for Research on Ebola Virus in Liberia) – collaboration between Liberian MOH and U.S. HHS**
- **Ebola studies**
  - PREVAIL I: Phase 2 placebo-controlled vaccine trial
  - PREVAIL II: SOC vs SOC + ZMapp treatment trial
  - PREVAIL III: Natural history of survivors
  - PREVAIL IV: GS-5734 for persistent virus in semen
  - PREVAIL V: Phase 2 RCT of Ad26.ZEBOV/MVA-BN-Filo and rVSVΔG-ZEBOV-GP

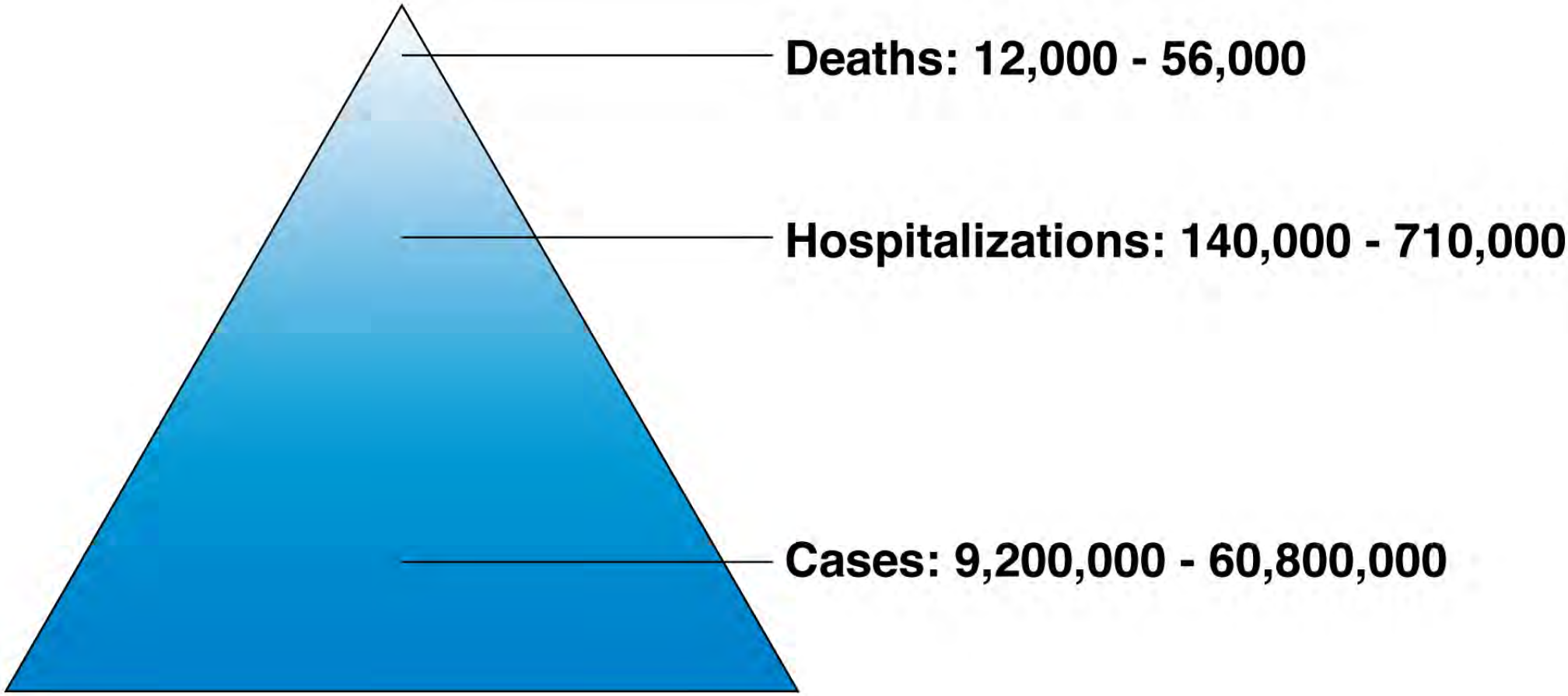
# New Ebola Outbreak in Democratic Republic of the Congo (DRC), April-May 2017

- 19 suspected cases, 3 deaths (as of 5/15/2017)
- Bas-Uélé province, >1,300 kilometers from Kinshasa
- 8th Ebola virus disease epidemic in DRC since 1976

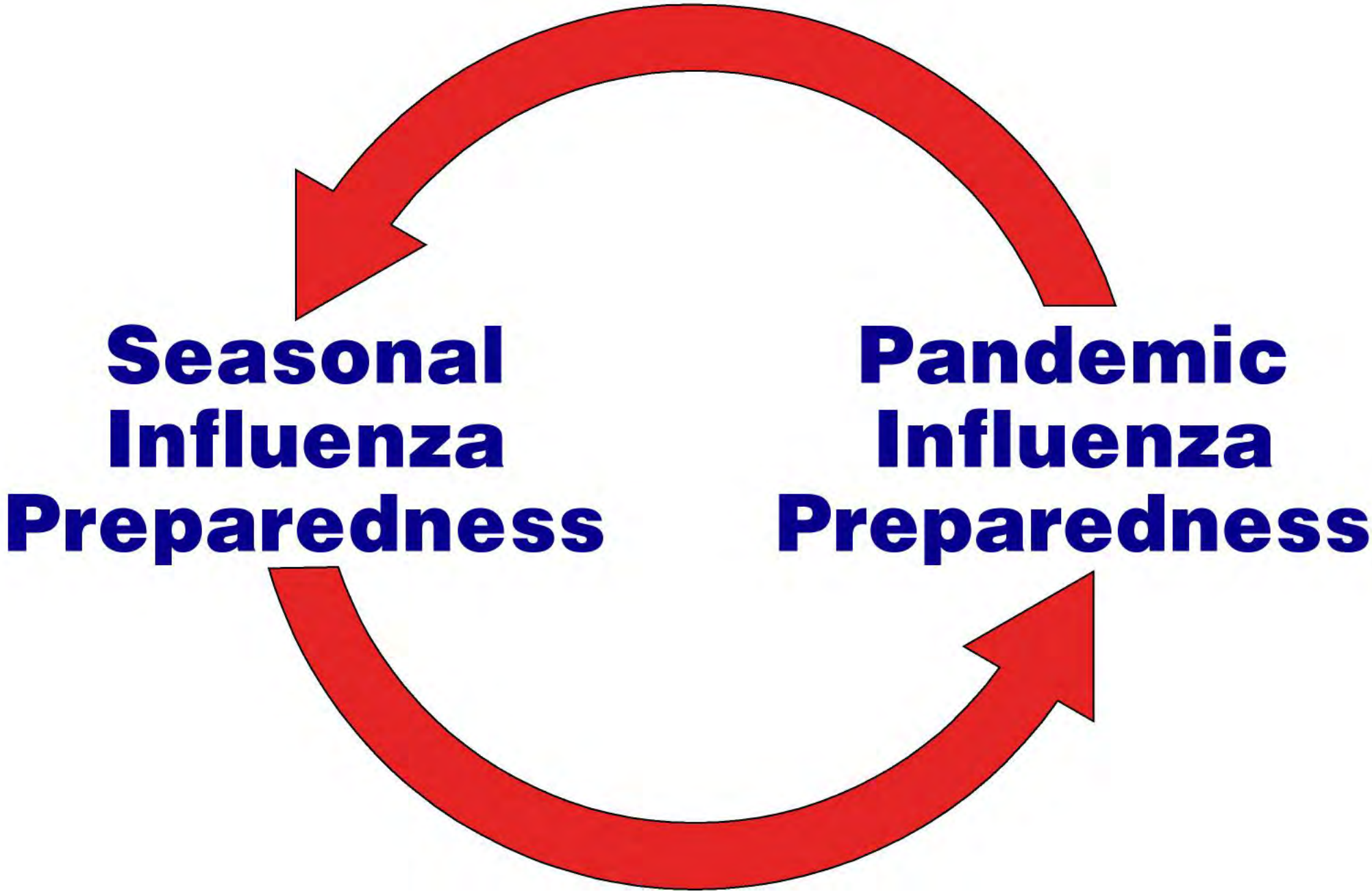
# INFLUENZA IN THE 20TH CENTURY



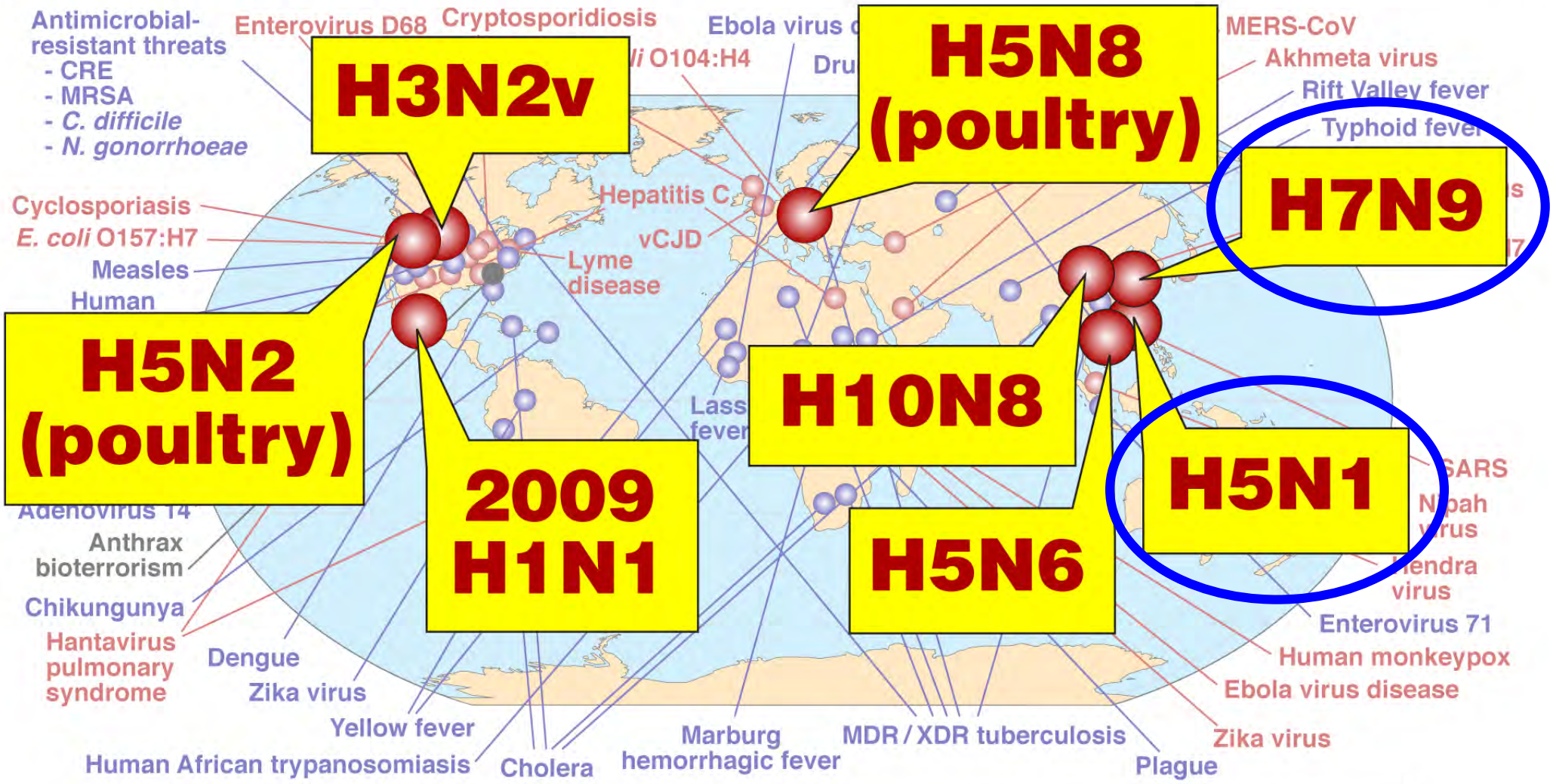
# Annual Disease Burden of Influenza in the United States




Source: CDC. Annual estimates since 2010


Seasonal
Influenza
Preparedness
Pandemic
Influenza
Preparedness

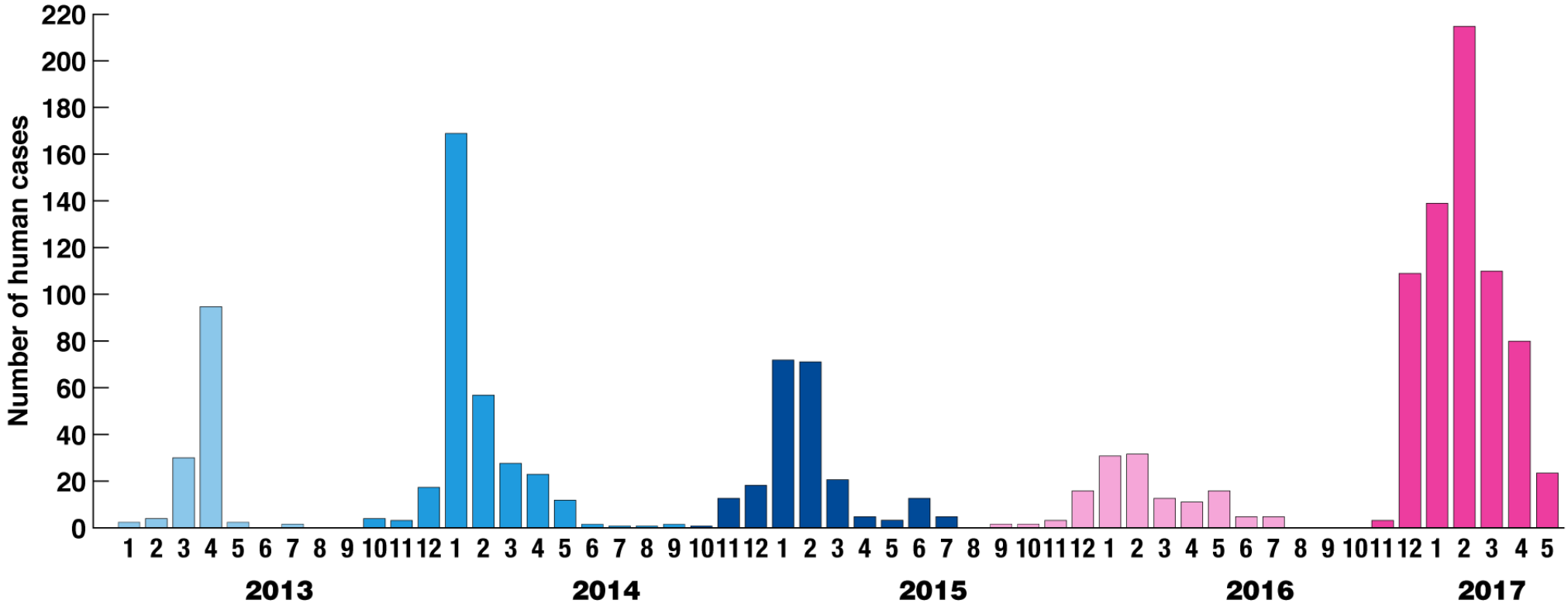
# Examples of Recently Emergent Influenza Viruses




December 2016

# Five Waves of Human H7N9 Influenza Infections in China, February 2013-present

- **1,486** confirmed human cases, **559** deaths
- 5th wave: >40% of cumulative cases

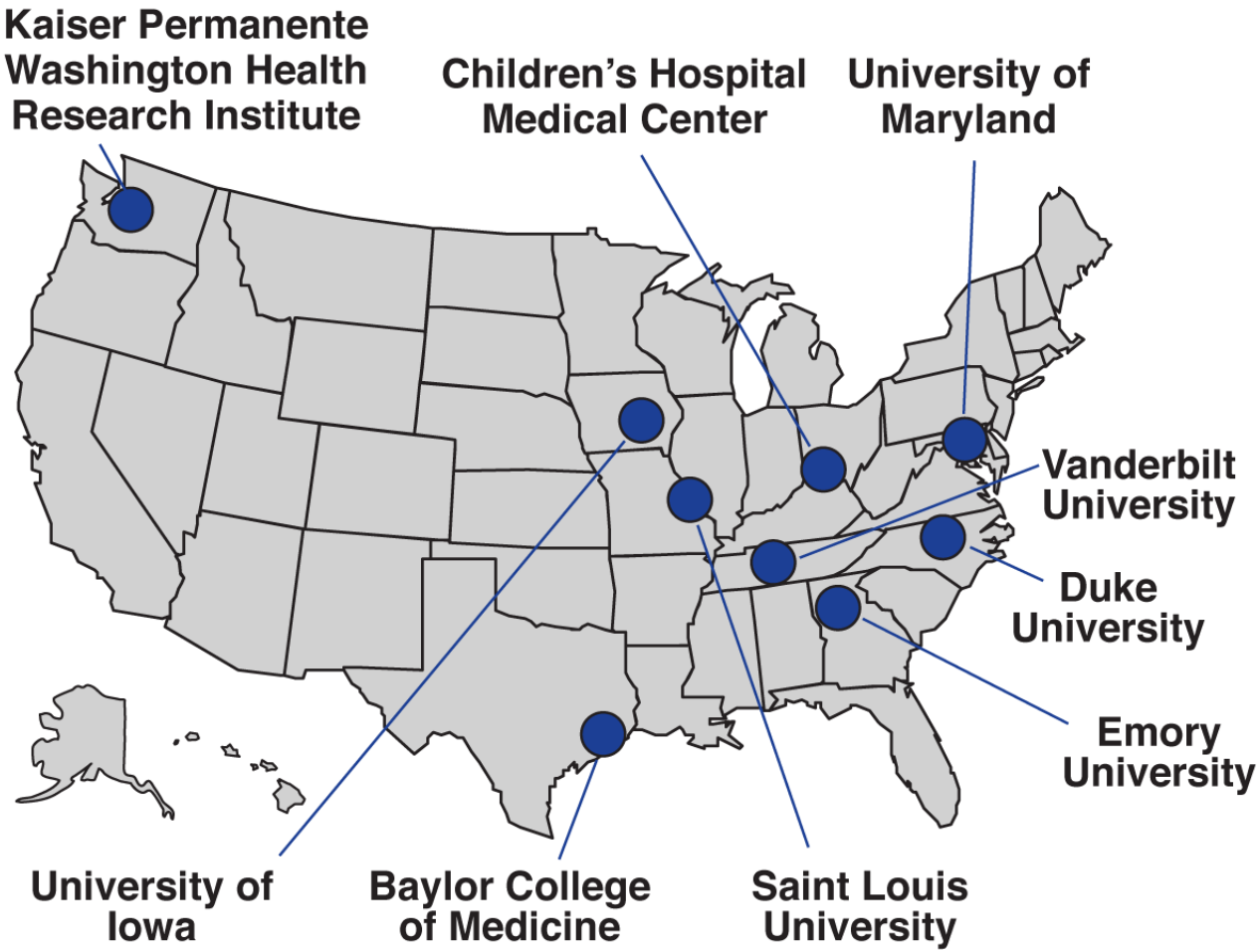



Source: FAO, 5/10/2017

# NIAID H7N9 Influenza Proposed Vaccine Trials

- Phase 2 trials (several hundred volunteers) evaluating safety and immune response
  - Healthy Adults
  - Elderly
  - Children
  - Pregnant Women
  - Mix and Match (Vaccine from Company A + Adjuvant from Company B)
  - Concomitant with Seasonal (Adults)
  - Concomitant with Seasonal (Children)
- Trials would be conducted via the NIAID Vaccine and Treatment Evaluation Units (VTEUs)

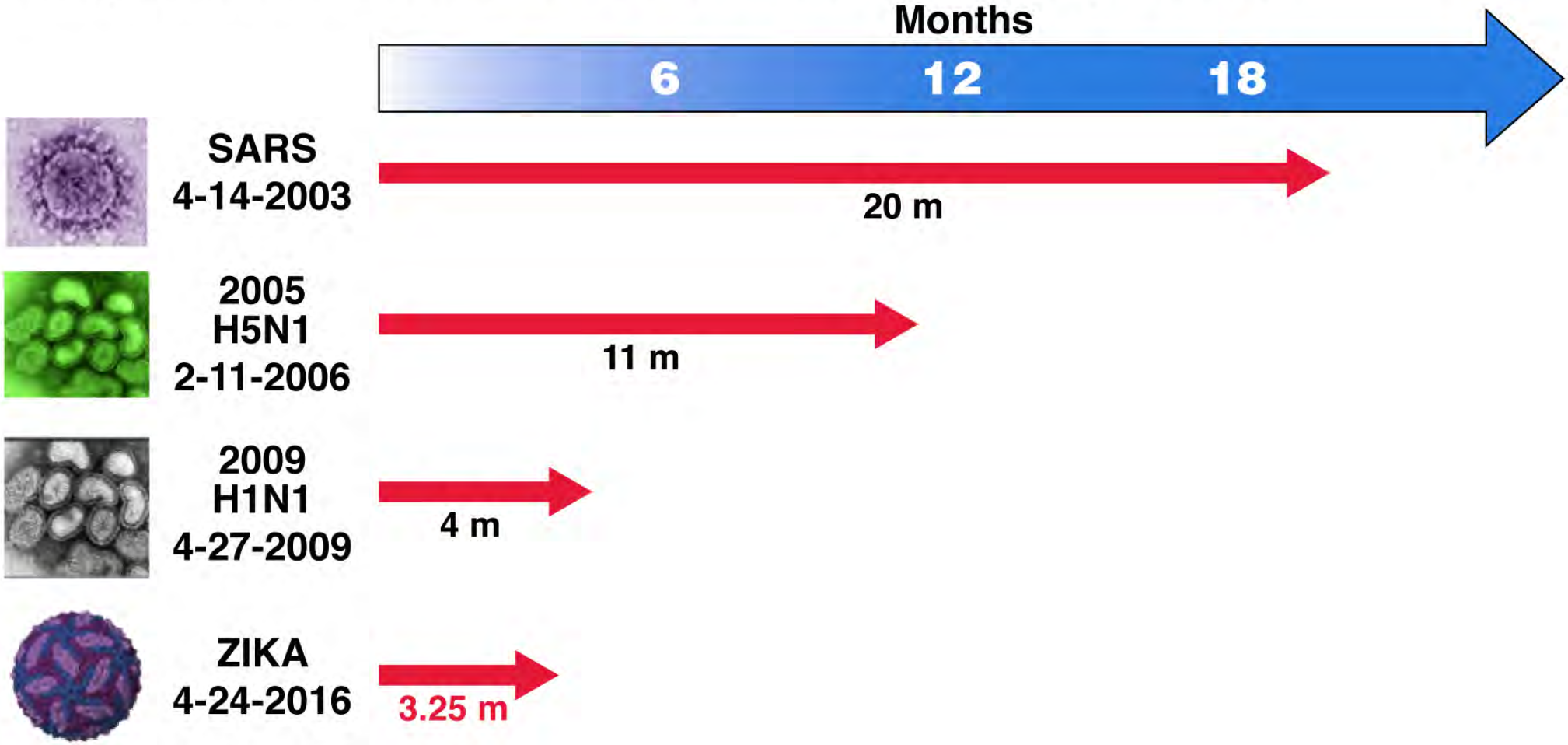
# NIAID Vaccine and Treatment Evaluation Units (VTEUs)




- Established in 1962
- Clinical trials to evaluate vaccines, diagnostics and therapeutics
- Epidemiologic studies
- Access to healthy and sick populations
  - Pediatric
  - Adult
  - Elderly
- Domestic and international capabilities

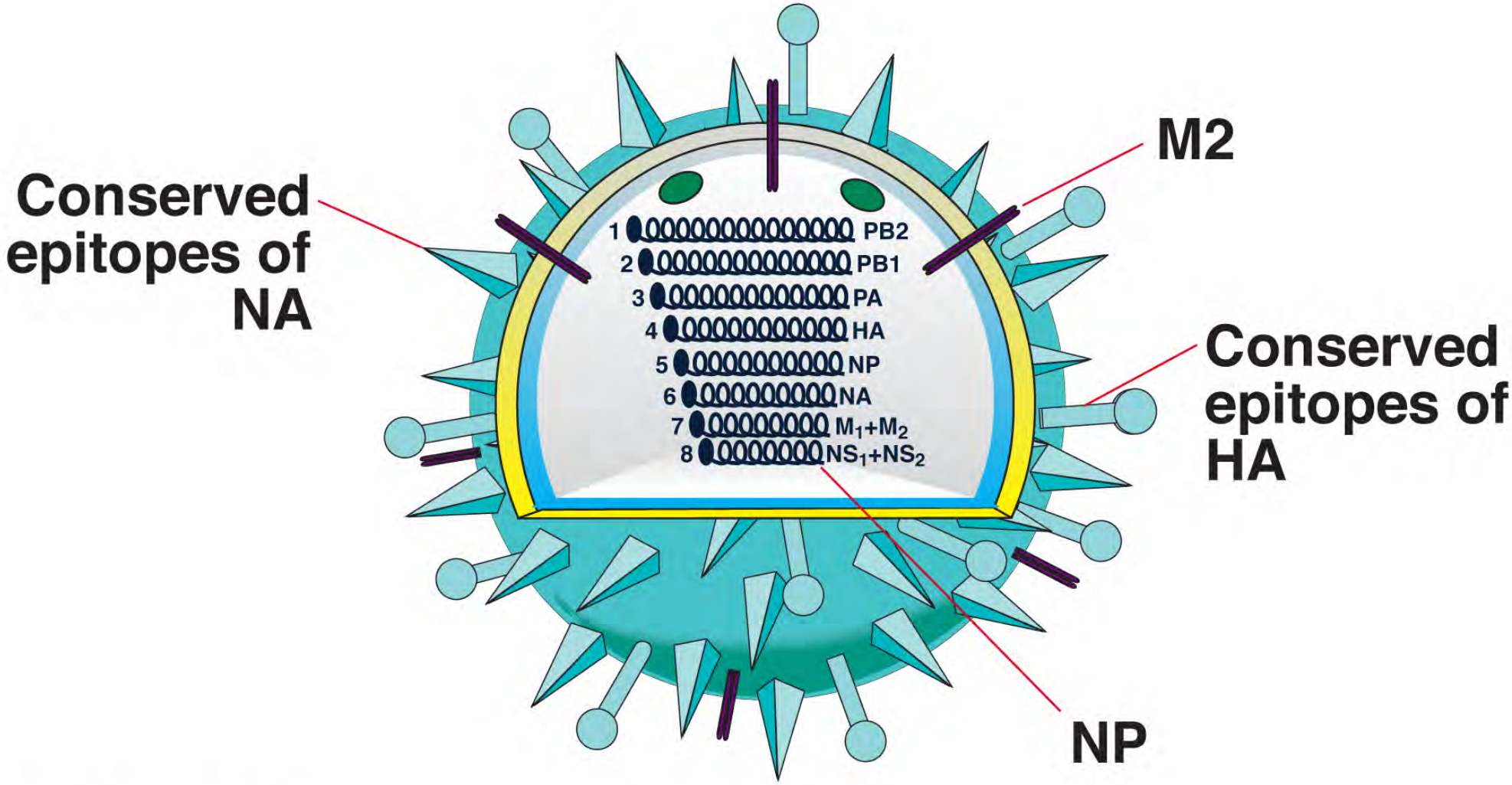
# VRC DNA Vaccines for Emerging Infections

## Sequence Selection to 1st Human Injection



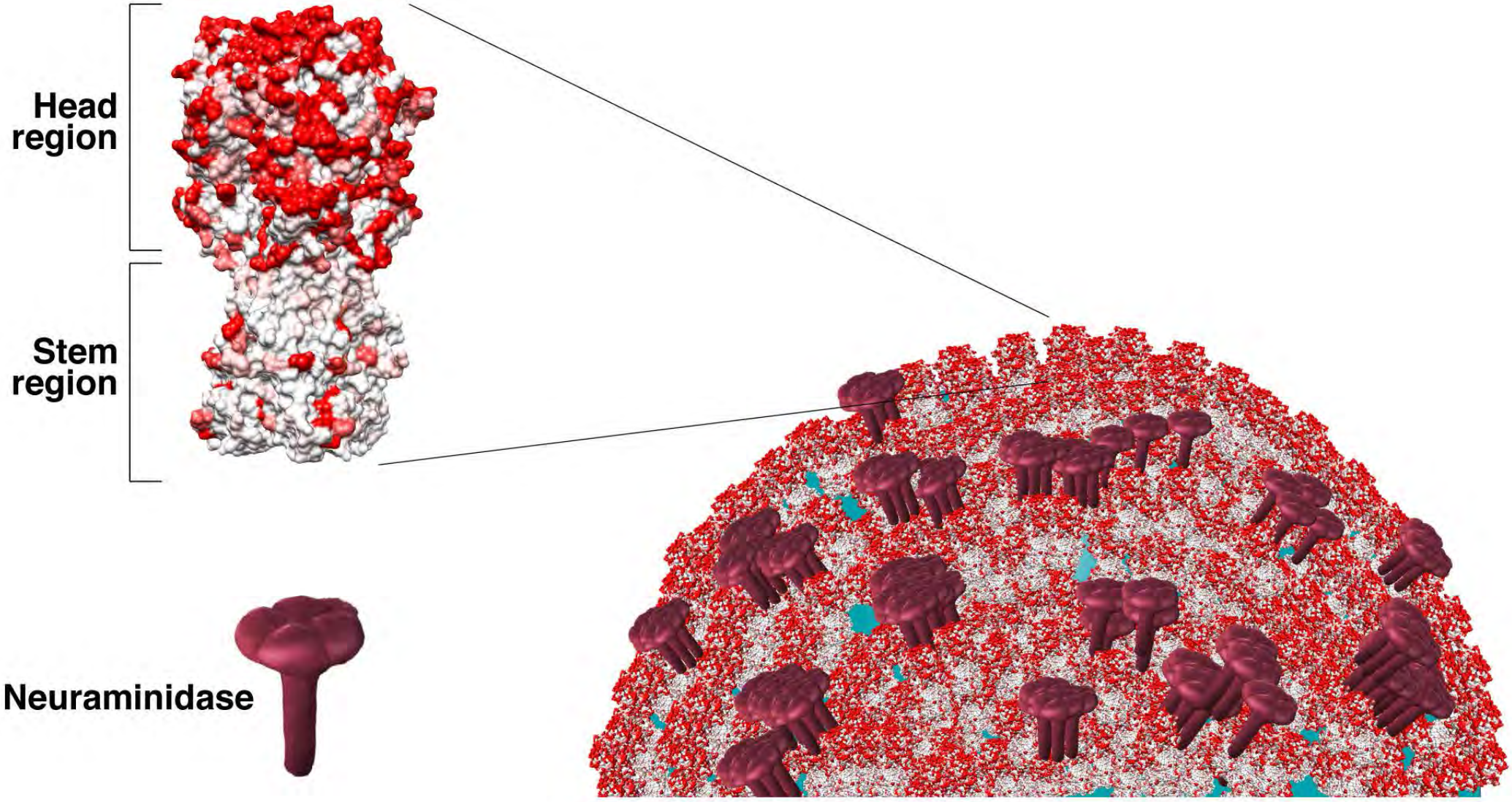

Courtesy: J Ledgerwood/NIAID VRC

# Selected Targets for "Universal" Influenza Vaccines

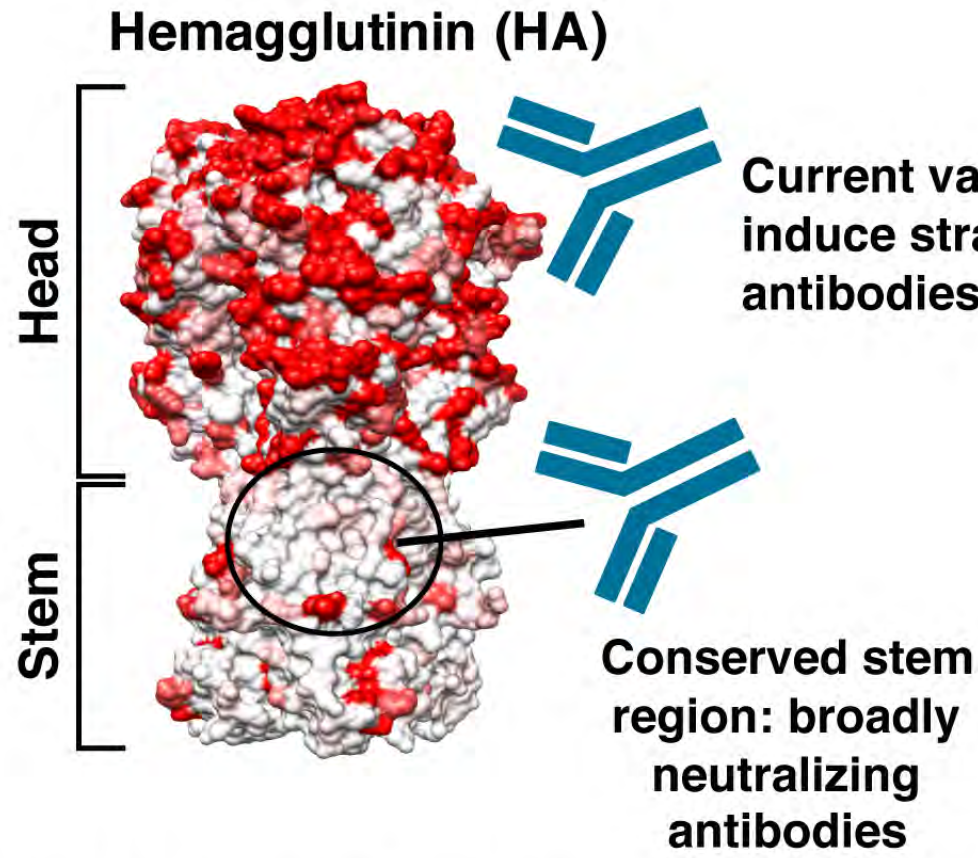



Source: Subbarao/Murphy

# Influenza A Hemagglutinin (HA)



# Generating Broadly Neutralizing Antibodies: Targeting the Stem




Courtesy Jeffrey Boyington

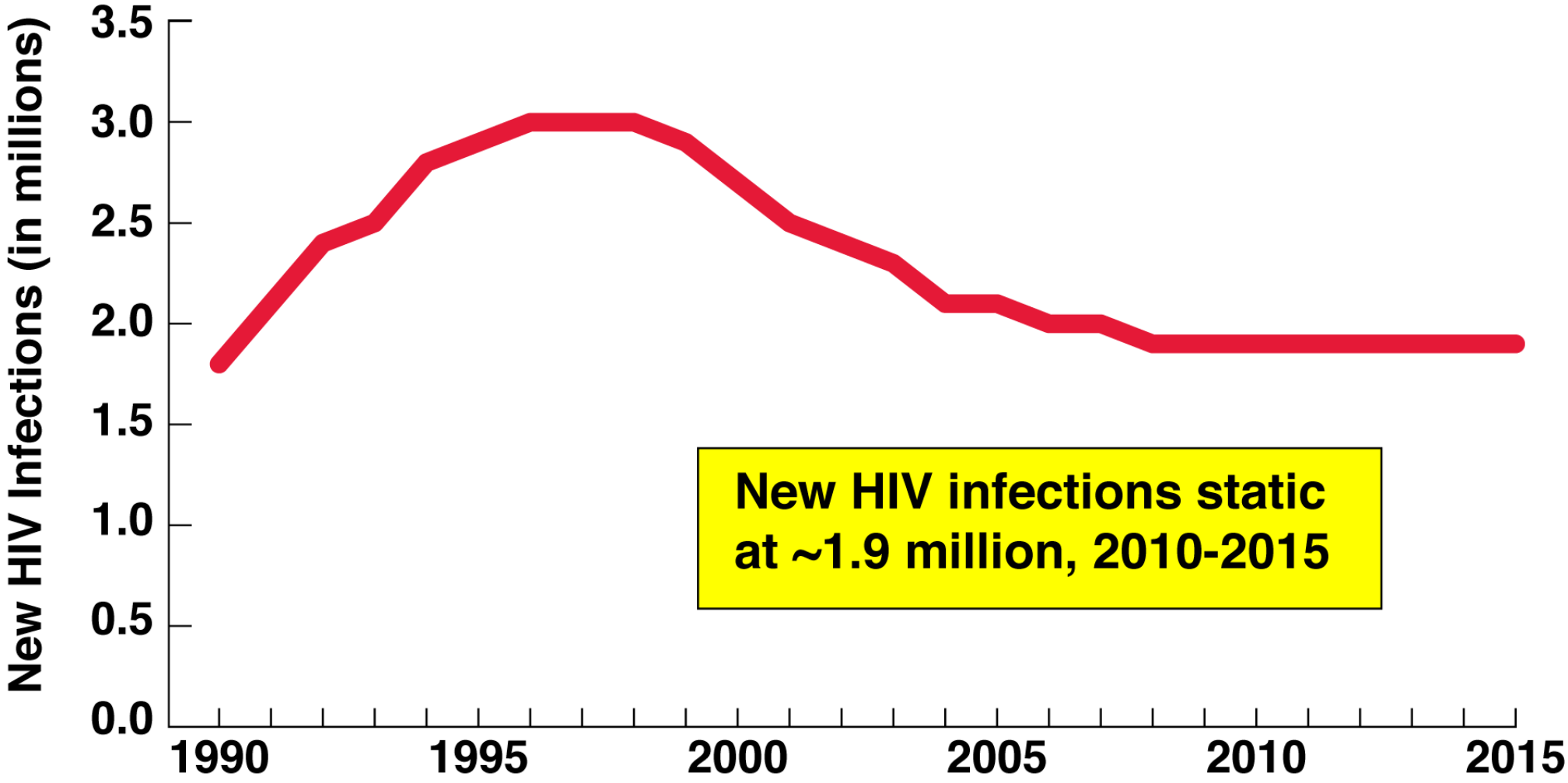
- Most antibodies bind to epitopes of highly variable head region
- Antibodies that neutralize multiple strains bind to a highly conserved area in the stem region

# Examples of Established Infectious Diseases of Global Health Importance

| | Estimated Deaths, 2015 |
|---|---|
| Lower Respiratory Infections | 3.2 M |
| Tuberculosis | 1.4 M |
| Diarrheal Diseases | 1.4 M |
| Hepatitis B & C | 1.3 M |
| HIV/AIDS | 1.1 M |
| Malaria | 429,000 |
| Meningitis | 315,000 |

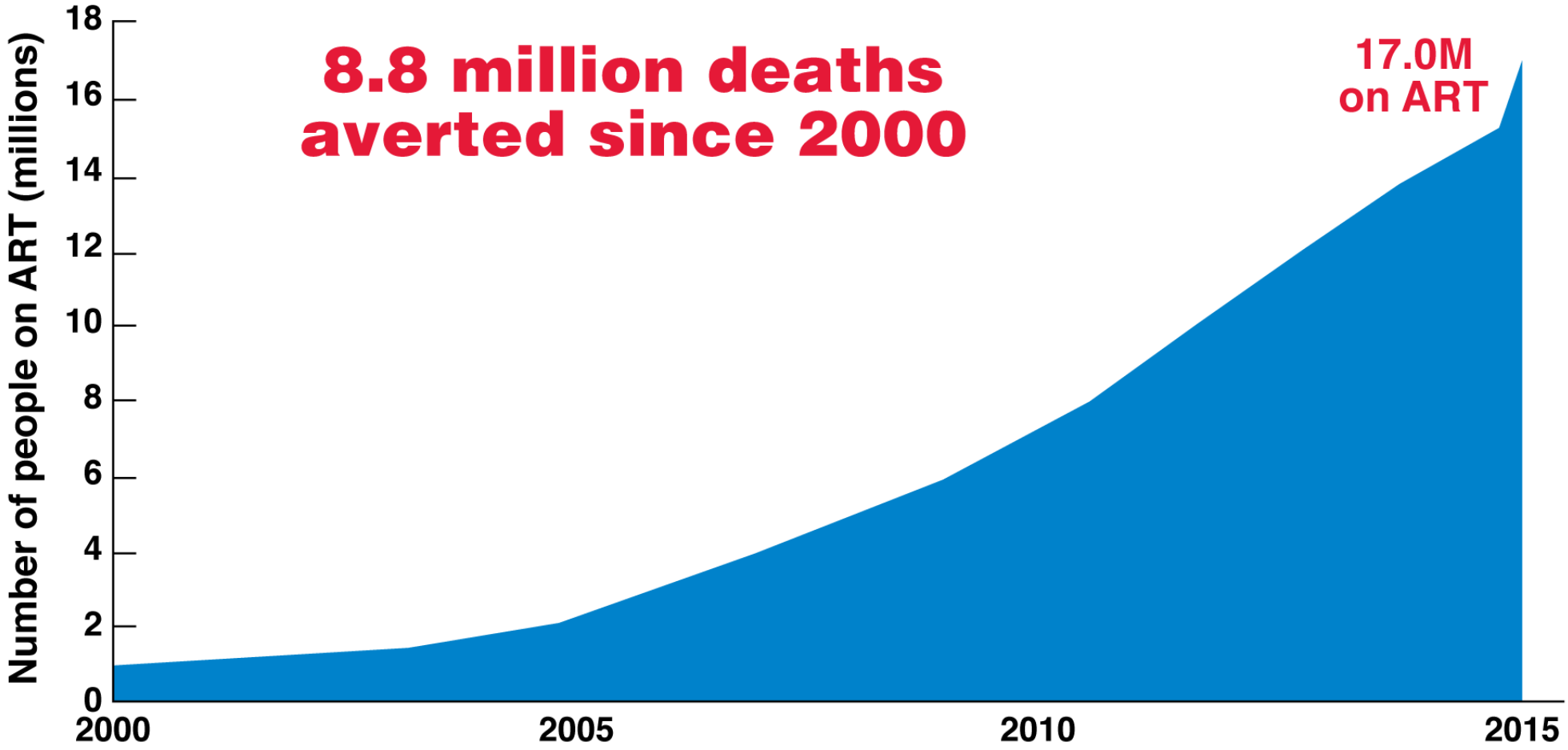
Source: WHO, 2017.

# New HIV Infections Globally Among People Aged ≥15 Years, 1990-2015



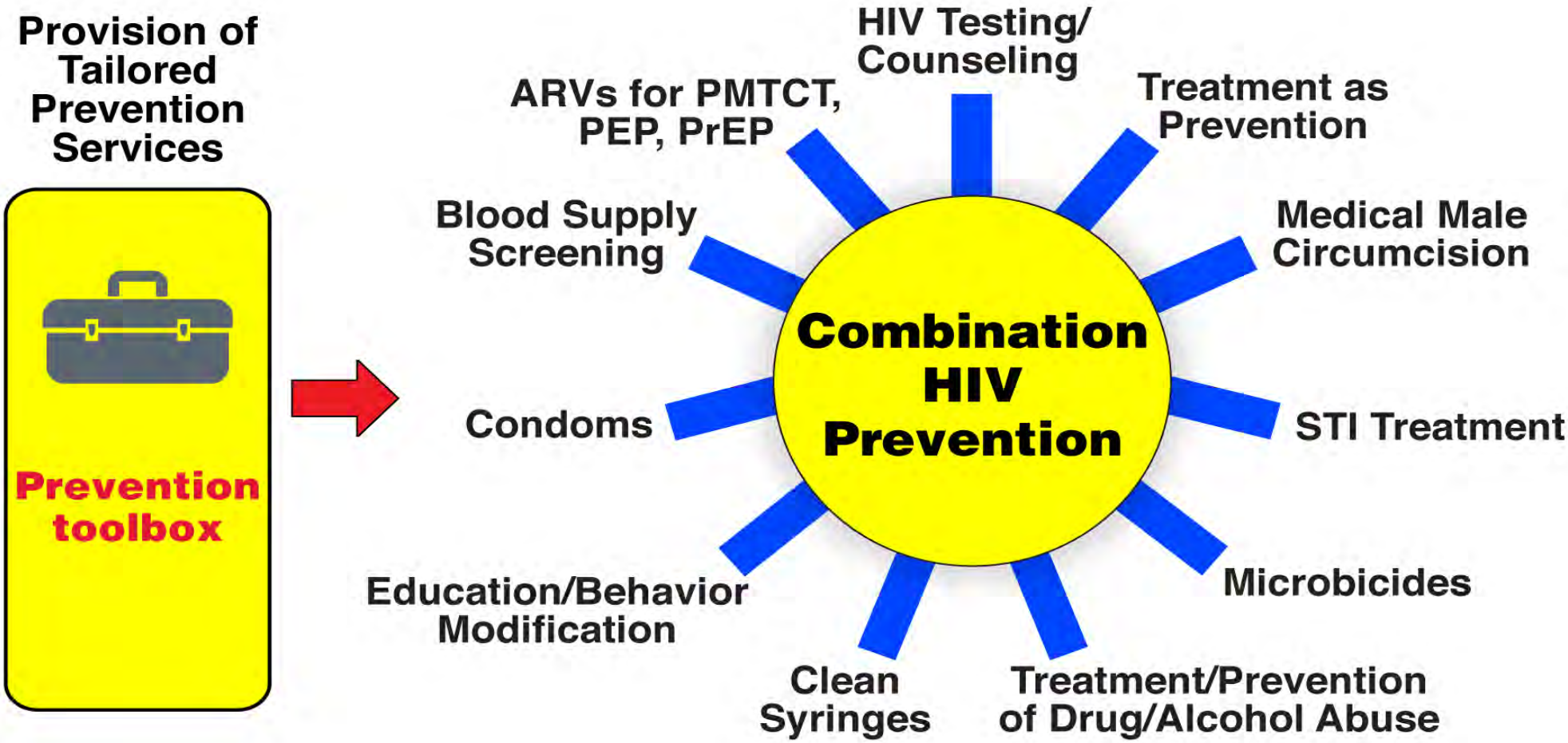

Source: UNAIDS, 2016

# Number of HIV-Infected People Globally Receiving Antiretroviral Therapy (ART), 2000-2015



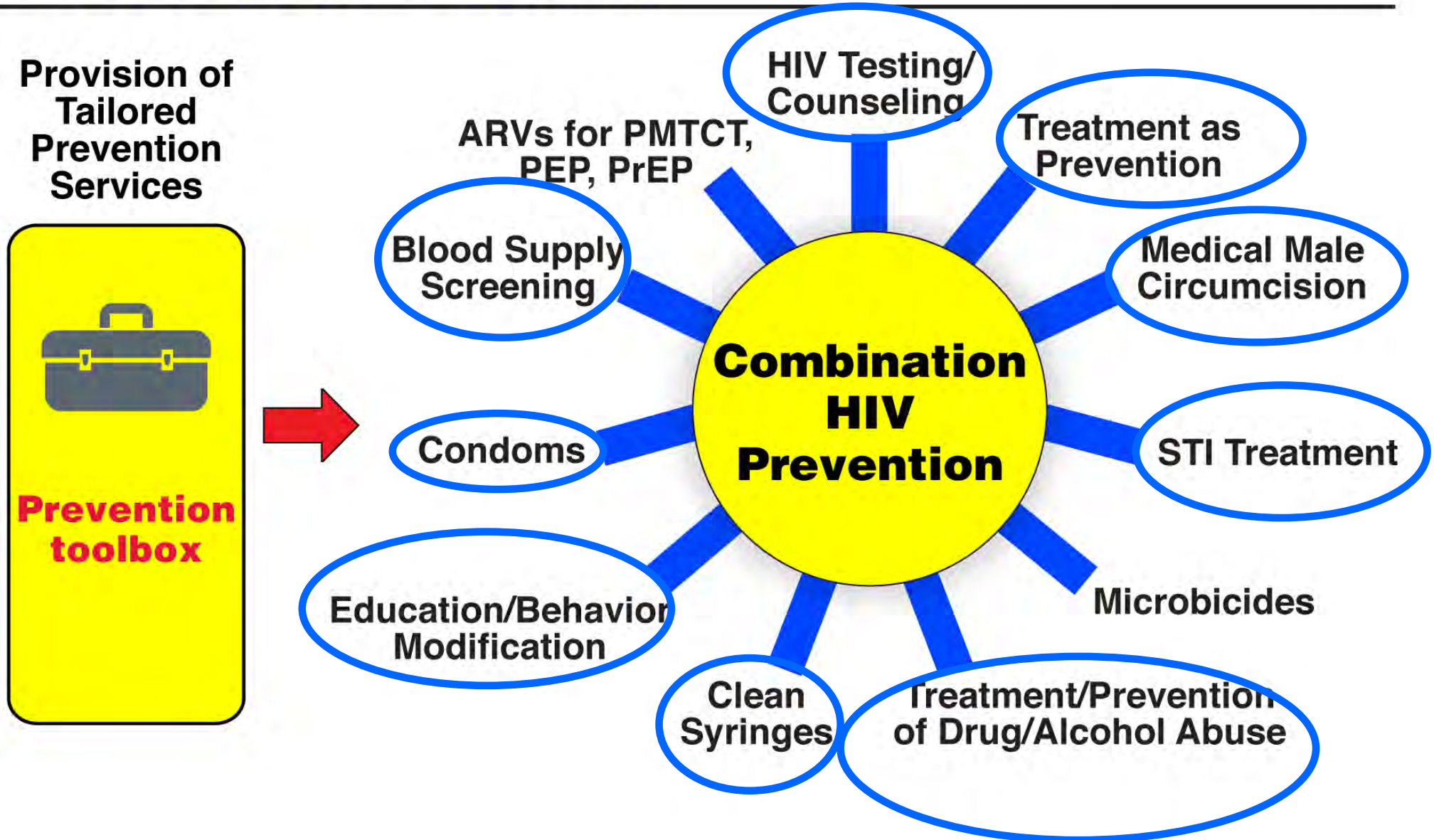

Source: UNAIDS, 5/2016

# Tailored Prevention Using HIV Prevention Toolkit




Extra Credit: How many of these are standard public health approaches?

# Tailored Prevention Using HIV Prevention Toolkit (Almost all Public Health!)



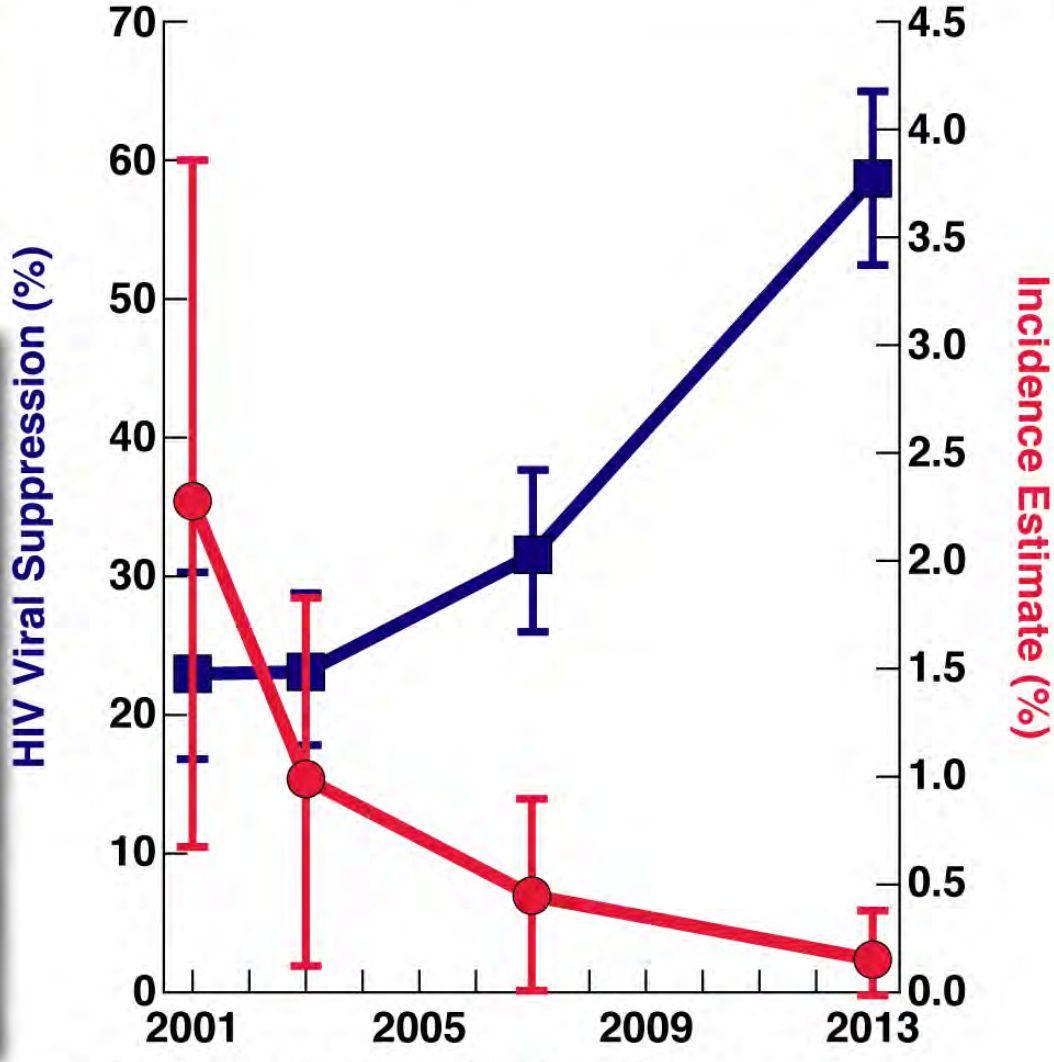
# Prevention Modalities Built upon Antiretroviral Therapy

- **Treatment as Prevention**
- **Pre-Exposure Prophylaxis (PrEP)**
- **Post-Exposure Prophylaxis (PEP)**
- **Prevention of Mother-to-Child Transmission**

# Treatment as Prevention in Baltimore


**Improvements in the Continuum of HIV Care in an Inner-City Emergency Department**

GD Kelen, TC Quinn et al.




- As viral suppression increased from 23% to 59%, HIV incidence decreased from 2.3% to 0.16%

# Prevention Modalities Built upon Antiretroviral Therapy

- Treatment as Prevention
- Pre-Exposure Prophylaxis (PrEP)
- Post-Exposure Prophylaxis (PEP)
- Prevention of Mother-to-Child Transmission

# HIV Pre-Exposure Prophylaxis (PrEP)

- HIV PrEP is the use of an antiretroviral medication to prevent the acquisition of HIV infection by at-risk uninfected persons

- Oral Truvada® (emtricitabine and tenofovir disoproxil fumarate) is licensed for HIV PrEP in the USA

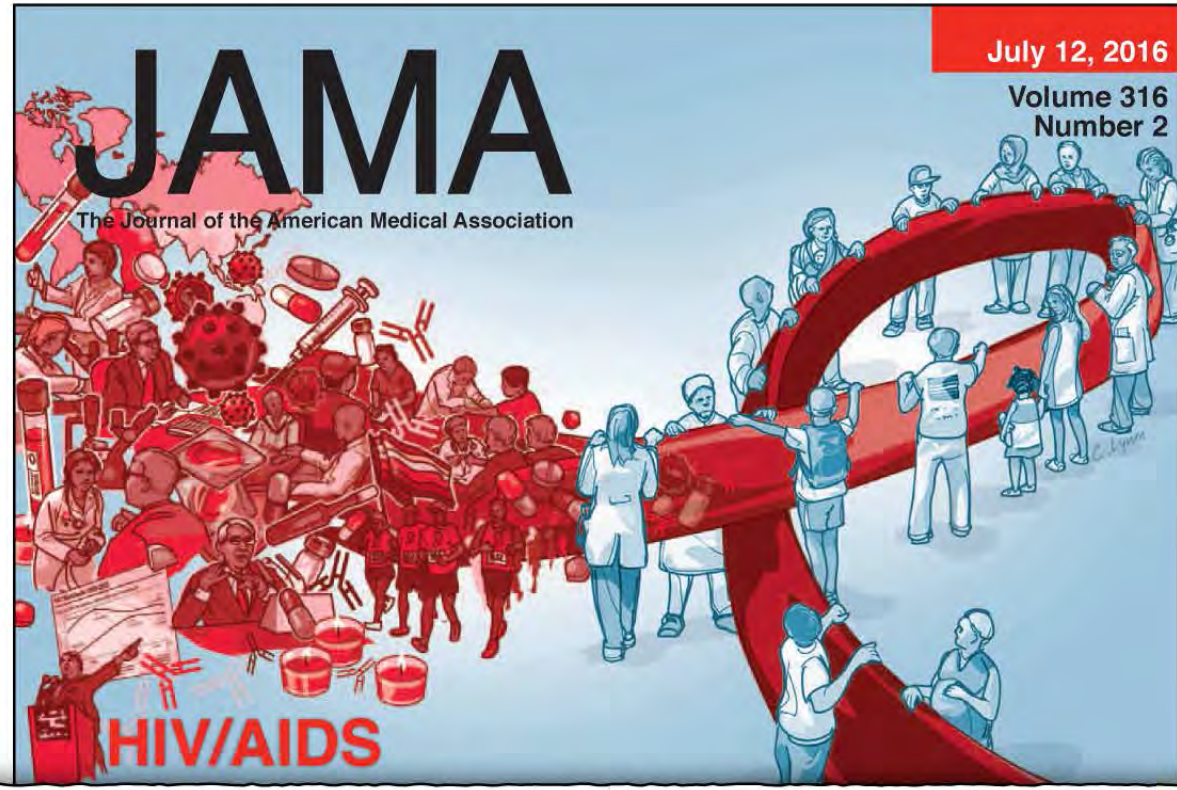

National Institutes of Health
*Turning Discovery Into Health*

FOR IMMEDIATE RELEASE
Tuesday, December 20, 2016

**News Release**

# NIH Launches First Large Trial of a Long-Acting Injectable Drug for HIV Prevention

- **HPTN 083 will assess efficacy/safety of injected cabotegravir once every 8 weeks compared to daily oral PrEP with Truvada**
- **N= 4,500 MSM and TSM; 45 sites in eight countries in the Americas, Asia and Africa**



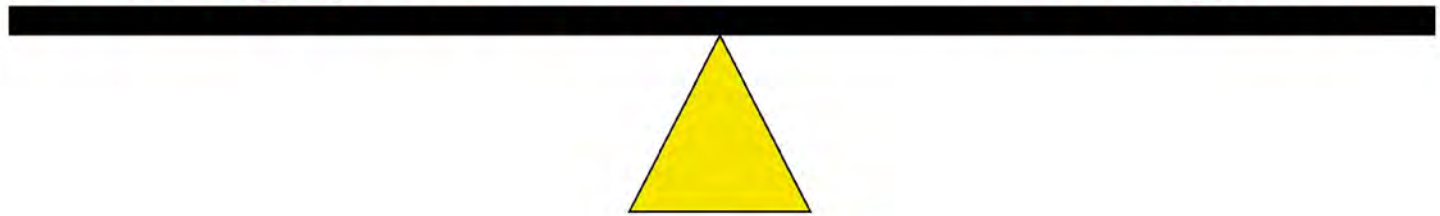

# An HIV Vaccine -- Mapping Uncharted Territory

AS Fauci

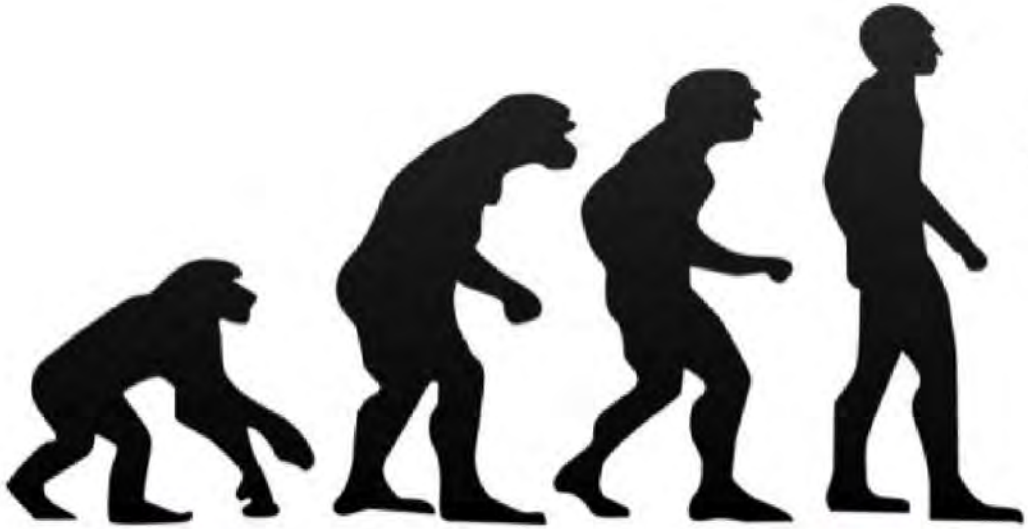
# Emerging and Re-emerging Infectious Diseases – A Delicate Balance

**The Extraordinary Capability of Microbial Pathogens to Change, Adapt, Emerge, Re-Emerge, and Persist**

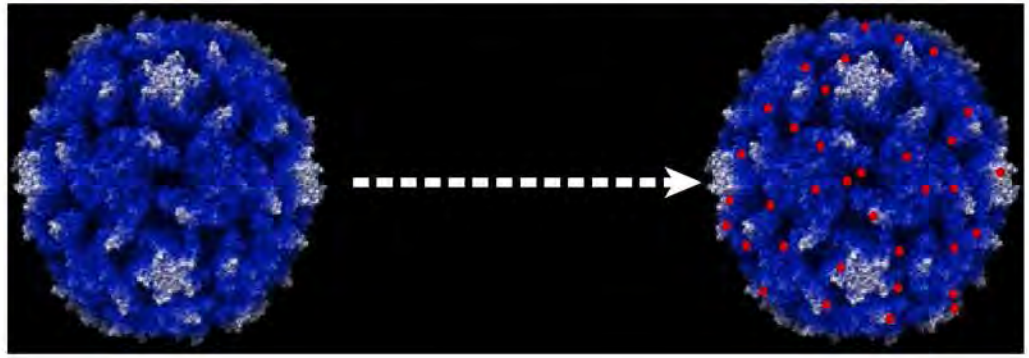
**Public Health Measures, Biomedical Research, and Countermeasure Development**



# Microorganisms versus Man



*Homo sapiens*
~8 million years
2% genome change



Human virus
<one day
2% genome change

**"The future of humanity and microbes likely will unfold as episodes of a suspense thriller that could be titled *Our Wits Versus Their Genes*."**

**--Joshua Lederberg, *Science*, April 14, 2000**

# THANK YOU

David M. Morens, MD, NIAID, NIH